

# Basic Histology Flash Cards

MESCHER

# Basic Histology Flash Cards

200 high-yield full-color flash cards  
reinforce your knowledge of tissue  
identification and function

Anthony L. Mescher, PhD

- 200 cards with full-color illustrations
- Sharpens your ability to identify structures
- Details the characteristic features of each tissue and cell type
- Each card includes at least one major medical condition
- Enhanced by Key Points and Clinical Notes

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# Basic Histology

# Flash Cards

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## Preface

Flash cards summarizing basic information have proven to be an extremely effective tool for study and retention of knowledge in the biomedical sciences. The use of well-crafted flash cards, either as a guide in self-learning or as part of a partner or team-based approach to study, greatly facilitates active and efficient learning of basic concepts.

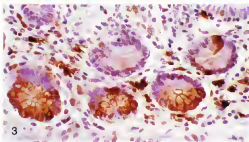
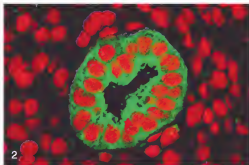
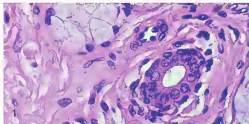
*Lange Basic Histology Flash Cards* offers a complete set of 200 cards that summarize fundamental points in every chapter in *Junqueira's Basic Histology: Text & Atlas*, 12th edition. One side of each card shows one or more color histologic images with key features marked for identification. The other side lists these structures and very concisely summarizes the **Key Points** to be learned regarding that tissue. Study of the characteristic features of each tissue and cell type, together with the **Key Points** one needs to know about those structures, provides an invaluable supplement to any textbook or lecture series presentation of histology. Each flash card also includes a brief **Clinical Note**, written to reinforce student understanding of that tissue's function and to indicate at least one medical condition or disease involving the tissue. Finally, every flash card cites the pages in *Junqueira's Basic Histology: Text & Atlas*, 12th edition, where a more complete explanation of that card's topic is provided.

Since its inception, *Junqueira's Basic Histology: Text & Atlas* has set the standard for a concise yet thorough presentation of tissue structure and function for students in the health professions and advanced undergraduates. Similarly, the various series of board reviews and study guides also published by McGraw-Hill/Lange, all written by medical educators with many years of teaching experience, are recognized as leading resources for student review and exam preparation. To this legacy of biomedical sciences learning resources from McGraw-Hill/Lange can now be added the new *Lange Basic Histology Flash Cards*. We are confident that users will find this new study aid a highly valuable, high-yield guide in their progress through basic histology.

**Anthony L. Mescher, PhD**

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Name the 3 staining techniques shown here.





# HISTOLOGICAL STAINING TECHNIQUES

1. Routine hematoxylin and eosin (H&E) staining
2. Immunofluorescent staining
3. Immunoperoxidase staining

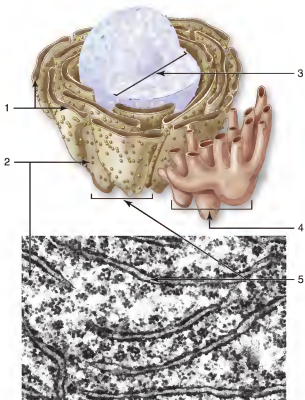
**Key Points:** H&E staining is the most widely used method of preparing slides for bright-field microscopy. Basophilic structures such as cell nuclei stain dark blue or purple by this method, whereas acidophilic material such as collagen and many cytoplasmic proteins stain pink-orange. H&E staining can be used successfully to study a wide variety of tissue types and organs.

Fluorescent stains conjugated to antibodies allow highly specific localization of the proteins that the antibodies recognize. Visualized using a fluorescent microscope at the wavelength of the stain, this immunofluorescent preparation was made with a green fluorescent compound bound to antibodies against an epithelial integrin. The cytoplasm of the epithelial cells shown here is stained green, but not the cytoplasm of neighboring fibroblasts. However, the nuclei of all the cells are stained red by the DNA-binding propidium iodide also used here.

Antibodies linked to the enzyme peroxidase allow the specificity of **immunohistochemistry** to be used with bright-field microscopes. This indirect immunoperoxidase preparation used primary antibodies against the enzyme lysozyme. Peroxidase-conjugated secondary antibodies are prepared against the immunoglobulin class of the primary antibodies. When provided with its substrate, peroxidase yields a brown reaction product specifically over the lysozyme-containing Paneth cells and macrophages in and around the intestinal glands seen here.

**Clinical Note:** Although H&E staining is routinely used in most hospital pathology laboratories, immunohistochemistry is used to study specimens containing specific proteins, such as certain classes of tumors or virus-infected cells, using antibodies against the proteins specific for the tumor or virus. The immunoperoxidase staining technique allows the use of the simpler and less expensive bright-field microscope.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 3 and 12-14.*



## NUCLEUS AND ENDOPLASMIC RETICULUM

1. Cisternae of endoplasmic reticulum (ER)
2. Ribosomes
3. Nucleus
4. Smooth endoplasmic reticulum (SER)
5. Rough endoplasmic reticulum (RER)

**Key Points:** Newly made mRNA leaves the **nucleus** via nuclear pores and begins to be translated into proteins on **ribosomes**. Proteins to be secreted or destined for membrane insertion contain signal peptides in their sequence emerging initially from the ribosomes. Such amino acid sequences are bound by signal recognition proteins, which in turn bind receptors on **rough endoplasmic reticulum (RER)**. This allows the newly translated protein to be translocated through the membrane into the RER cisterna as it is synthesized by the ribosome. RER also contains enzymes and chaperone proteins, which respectively mediate the initial posttranslational modifications and the correct folding of the new proteins.

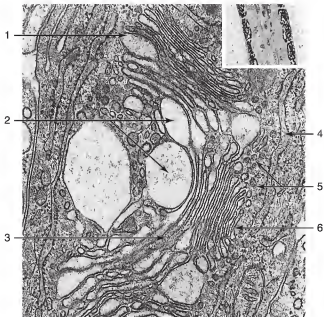
Free polyribosomal complexes, which are translating proteins without signal sequences and therefore not bound to RER, generally synthesize cytoplasmic proteins such as cytoskeletal proteins, nuclear and ribosomal proteins, and the many enzymes of cytoplasm.

**Smooth ER** lacks membrane proteins for binding signal peptides and therefore lacks polyribosomes on its surface and appears smooth by transmission electron microscopy. Membranous cisternae of SER include enzymes that allow the following functions:

- Synthesis of steroids and other complex lipids (well developed in cells of adrenal cortex)
- Degradation of potentially noxious low molecular weight compounds that have been ingested (an especially important function in liver cells)
- Sequestration and controlled release of  $\text{Ca}^{2+}$  within the cytoplasm (a function required for the function of muscle cells)
- Glucose release from glycogen (using the enzyme glucose-6-phosphatase)

**Clinical Note:** A frequent cause of jaundice in newborn infants is the underdeveloped state of SER in liver cells. Fully differentiated, the SER of such cells includes enzymes for the conversion of bilirubin to a water-soluble form that is readily excreted.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 328-330.*



## GOLGI APPARATUS

1. Dilated Golgi apparatus transport vesicle
2. Forming secretory granules
3. *Trans* or exit face of Golgi apparatus
4. Rough endoplasmic reticulum (RER)
5. Transport vesicles from RER
6. *Cis* or entry face of Golgi apparatus

**Key Points:** Vesicles separating from **cisternae of RER** and containing partly modified proteins move to the nearby **Golgi apparatus** where the proteins are processed further. Ultrastructurally, the Golgi complex appears as a stack of membranous saccules, often near the cell nucleus. With the light microscope, the Golgi apparatus is best visualized histochemically using enzymes specifically located in this organelle, as shown in the inset in the figure.

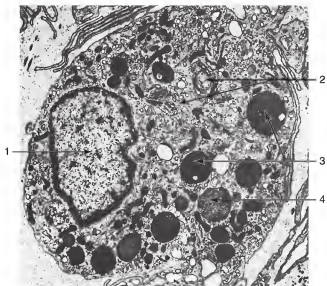
The **transport vesicles** from the RER merge with vesicles comprising the *cis*, entry, or forming face of the Golgi complex to produce the first of the stacked saccules. Specific enzymes on the *cis* face of the **Golgi apparatus** further modify the newly arrived proteins. For additional protein modifications, new transport vesicles pinch from the edges of the initial saccules and merge with membranes deeper in the Golgi where other enzymes are located. Sorting of the modified proteins into transport vesicles destined to form secretory granules, to form certain membranous organelles such as lysosomes, or for other functions occurs in medial and *trans* regions of the **Golgi apparatus**.

Specific functions of the Golgi apparatus include:

- Glycosylation, phosphorylation, and hydroxylation of specific amino acids in proteins
- Protein folding and formation of disulfide bonds between specific cysteine side chains in specific proteins
- Sorting the modified proteins and packaging them for use in lysosomes, for secretion, and for incorporation into the cell membrane

**Clinical Note:** A common form of cystic fibrosis is due to genetic mutations that affect a protein forming a chloride ion channel. The resulting protein cannot be properly folded or glycosylated in the Golgi apparatus. The defective chloride ion channels lead to physiological changes, including production of excessively thick mucus in the respiratory system.

See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 30-34.



## LYSOSOMES

1. Cell nucleus
2. Golgi complexes
3. Primary lysosome
4. Secondary lysosome (heterolysosome or phagolysosome)

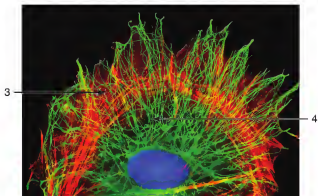
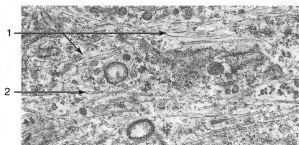
**Key points:** Lysosomes are membrane-bound organelles in which phagocytosed material and certain defective cytoplasmic structures are broken down and digested. Formed in the **Golgi apparatus**, lysosomes contain 40 to 50 different acid hydrolases and are particularly abundant in cells specialized for phagocytosis, such as neutrophils and macrophages.

**Primary lysosomes** are typically spherical, uniformly electron dense, and vary in diameter from 20 to 50 nm. These lysosomes fuse with vacuoles containing material ingested during phagocytosis to produce **secondary lysosomes**, which have less uniform contents than primary lysosomes. Fusion brings to the secondary lysosome  $H^+$  ATPases in the vacuolar membrane that pump protons into the structure. This lowers the pH of the secondary lysosome to approximately 5.0 and activates the lysosomal acid hydrolases. Released subunits of the ingested proteins, lipids, and nucleic acids are recycled, and any indigestible material remains in the final condensed vesicles termed residual bodies.

Unneeded or nonfunctional cytoplasmic structures and organelles can be enclosed by membrane and fused similarly with primary lysosomes. The resulting structures are called autophagosomes, and this mechanism of removing organelles is called autophagy.

**Clinical Note:** In the so-called lysosomal storage diseases, one or more of the hydrolytic enzymes is nonfunctional usually as a result of a mutation in the gene encoding the enzyme. Such a defect causes undigested substrate to accumulate in secondary lysosomes, which can eventually disrupt cellular function in long-lived cells such as neurons. Examples are Tay-Sachs disease and Niemann-Pick disease, in which hexosaminidase A and sphingomyelinase are defective, respectively.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 32-35.*





# CYTOSKELETON

- 1, 3. Microfilaments (or actin filaments)
- 2, 4. Microtubules

**Key Points:** The cytoskeleton serves the following general functions:

- Determines cell shape
- Mediates changes in cell shape during phagocytosis, cytokinesis, and other processes
- Forms supporting tracks for the movement of organelles and cytoplasmic vesicles by motor proteins within cells

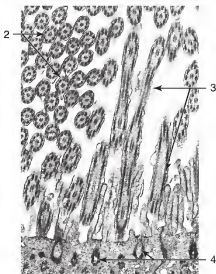
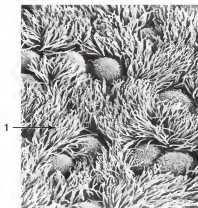
The cytoskeleton contains three types of structures, each composed of protein polymers:

- **Microtubules** are hollow, fairly rigid structures with an outer diameter of 24 nm composed of polymerized heterodimers of  $\alpha$  and  $\beta$  tubulin. Microtubules are dynamic structures, with tubulin polymerization promoted at microtubule organizing centers (MTOCs). One important MTOC is the pair of centrioles from which microtubules of the mitotic spindle are organized. Microtubules form one set of tracks for intracellular movements of membranous organelles and vesicles, mediated by the motor proteins kinesin and dynein.
- **Microfilaments (actin filaments)** are very thin (5-7 nm), highly dynamic filaments composed of actin subunits polymerized in a double-stranded helix. Usually, many microfilaments are present in parallel arrays or bundles, especially near the cell surface. Interactions of the actin filaments with myosin motor proteins produce localized changes in cell shape and provide another mechanism for movement of cytoplasmic components.
- **Intermediate filaments** are typically 10 to 12 nm in diameter (intermediate in size between microtubules and actin filaments). They are the least dynamic cytoskeletal component and function primarily in providing strong mechanical stability to cells. Intermediate filaments are composed of different proteins in different cells, including various keratins in different types of epithelial cells and three types of neurofilament proteins found in neurons.

**Clinical Note:** Certain classes of drugs widely used in **cancer chemotherapy** act by binding tubulin and blocking formation of functional mitotic spindles so that cells cannot divide.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 39-47.*

(Bottom image used with permission from Albert Tousson, University of Alabama-Birmingham High Resolution Facility.)



## CILIA

1. Cilia
2. Cilia in cross-section
3. Cilia in longitudinal section
4. Basal bodies

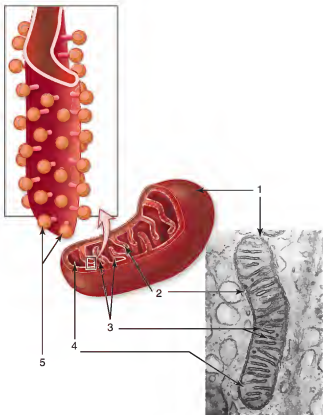
**Key Points:** Cilia are apical specializations abundant on some cuboidal or columnar epithelial cells that beat forcefully to move extracellular material such as mucus along the epithelial surface. They are particularly well developed on the pseudostratified columnar epithelium of the upper respiratory tract.

Within each cilium, microtubules are organized in an arrangement termed the axoneme, with nine doublets of microtubules organized around a central pair of microtubules. A series of paired “arms” composed of ciliary dynein project from each of the nine microtubule doublets and interact with tubulin subunits of the neighboring doublet. The dynein motor domains try to move along the microtubule with which they interact, which forces the adjacent doublets to slide relative to one another. Because such sliding is prevented by other proteins, the dynein-tubulin interaction produces a bending motion within the axoneme. This interaction, occurring very rapidly and sequentially around all nine doublets of the axoneme, causes the cilium to flail or beat in a rhythmic manner capable of moving material such as mucus lying across the cilia.

Each cilium is covered by the cell membrane and rooted at the cell surface in a **basal body**, a microtubule-organizing center containing nine triplets of microtubules. Growth occurs at the tip of a cilium, with tubulin, dynein, and other components transported distally and incorporated at the end of the axoneme.

**Clinical Note:** **Immotile cilia syndrome**, or **Kartagener syndrome**, is caused by a mutation in ciliary dynein that renders it nonfunctional. Among the medical problems associated with this syndrome are frequent respiratory tract infections caused by the inability to clear mucus and bacteria from the bronchi.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 42-43.*



## MITOCHONDRIA

1. Outer mitochondrial membrane
2. Inner mitochondrial membrane
3. Cristae
4. Matrix
5. Adenosine triphosphate (ATP) synthase complexes

**Key Points:** Mitochondria are organelles with two separate membranes and are the major sites for producing ATP, with usable energy stored in its phosphate bonds. Mitochondria are particularly abundant in metabolically active cells and in cytoplasmic regions specialized for various energy-requiring functions.

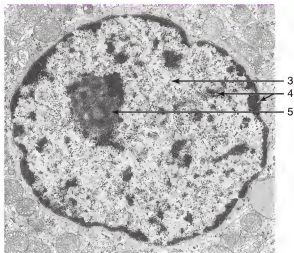
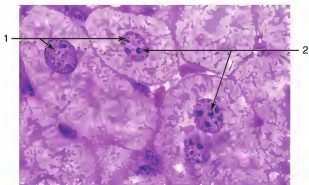
The **outer mitochondrial membrane** is smooth but porous, with transmembrane porins allowing easy passage to small molecules (<5000 daltons). The highly folded **inner mitochondrial membrane** has a much greater surface area and is very rich in proteins. These folds, or **cristae**, contain the enzymatic components of the electron transport system (respiratory chain). In high-resolution transmission electron microscopy (TEM), the inner surface of cristae shows the proteins of the **ATP synthase** systems as globular complexes on distinct stalks. The **matrix** enclosed within the inner membrane is also protein rich, containing enzymes for the citric acid cycle and fatty acid oxidation.

Release of mitochondrial proteins such as cytochrome c to the surrounding cytoplasm is an important event early in apoptosis and helps drive this process.

The mitochondrial matrix also contains a small circular DNA chromosome, along with ribosomes and other components needed for protein synthesis. The presence of these components allows synthesis of a few mitochondrial proteins semi-independently of the nucleus and supports the view that mitochondria may have arisen symbiotically with other cellular structures early in the evolution of eukaryotic cells.

**Clinical Note:** Myoclonic epilepsy with ragged red fibers (MERRF) is a rare disease occurring in individuals in whom cells of specific tissues, notably regions of skeletal muscle, inherit mitochondrial DNA with a mutated gene for lysine-tRNA, leading to defective synthesis of respiratory chain proteins that can cause structural abnormalities in these cells.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 25-27.*



## NUCLEI AND NUCLEOLI

1. Nuclei
2. Nucleoli
3. Euchromatin
4. Heterochromatin
5. Nucleolus

**Key Points:** A **nucleus** is a membrane-enclosed organelle that contains the cell's DNA in chromosomes or chromatin, from which all types of RNA are transcribed. Nuclei of growing cells and most differentiated cells are roughly spherical or oval shaped. The nuclei of cells active in protein synthesis usually contain one or more **nucleoli**, which are chromosomal regions with the heavily transcribed genes for ribosomal RNA. In these areas of the nucleus, abundant rRNA accumulates for processing and combining with ribosomal proteins, causing such regions to stain much more heavily, with either basophilic stains for light microscopy or electron-dense stains for transmission electron microscopy (TEM).

Ultrastructurally, nuclei of active cells usually show three kinds of chromatin:

- **Euchromatin** is rather uniformly lightly stained and contains chromatin that is dispersed for rapid, active transcription.
- **Heterochromatin** consists of small clumps of darkly stained chromatin and contains DNA that remains condensed due to lack of transcriptional activity. Heterochromatin is usually present immediately inside the nuclear membrane.
- **Nucleoli** appear as heterogeneous dark-staining areas in central regions of the nucleus. Staining differences within a nucleolus represent areas in which rRNA is being transcribed and areas in which the rRNA is combining with proteins to form ribosomal subunits.

Variations in the size and shape of nuclei are key features during many cellular changes, such as differentiation, mitosis, and apoptosis.

**Clinical Note:** Nuclei of cells in malignant tumors are often significantly enlarged, abnormally shaped, and extremely dark-stained compared with nuclei of normal cells nearby. Such nuclear features aid recognition of cancer cells by pathologists.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 48-52.*





## CELL JUNCTION COMPLEX

1. Tight junction (zonula occludens)
2. Adhering junction (zonula adherens)
3. Desmosome (macula adherens)

### Key Points: Tight junctions:

- Encircle most epithelial cells, typically at their apical ends.
- Form a seal preventing movement of most substances between the epithelial cells.
- Transmembrane proteins **claudin** and **occludin** interact between cells, producing the seal.
- Claudin and occludin link indirectly to cytoskeletal actin filaments via **ZO proteins**.
- Delimit the apical and basolateral domains of the epithelial cells by preventing movement of membrane proteins between these domains.

### Adhering junctions:

- Form strong adhesions between epithelial cells, helping produce a cohesive epithelial sheet.
- Also encircle epithelial cells, located just below the tight junctions.
- Transmembrane proteins of the **cadherin** family bind each other between cells, an interaction requiring  $\text{Ca}^{2+}$ .
- Cadherins link indirectly to cytoskeletal actin filaments via **catenins**.

### Desmosomes:

- Large singular, not circular, disk-shaped structures, occurring at numerous places between two cells.
- Form points of very strong adhesion between cells.
- Transmembrane proteins of the cadherin family (**desmoglein** and **desmocollin**) bind each other between cells.
- These proteins insert into cytoplasmic plaques containing **desmoplakin**, which in turn bind cytoskeletal intermediate filaments, principally those made of keratin, which are more stable than actin filaments.

**Clinical Note:** Various blistering diseases in skin are due to abnormal protein interactions within desmosomes. Causes include mutations that produce defective desmogleins or autoimmune reactions against specific desmogleins, either of which can result in loss of cell adhesion.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 67-69.*

What types of epithelia are shown here?



1

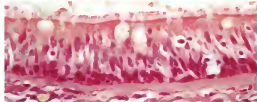
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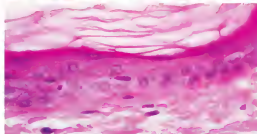
2



3



4



5

## TYPES OF EPITHELIA

1. Simple squamous epithelium
2. Simple cuboidal epithelium
3. Simple columnar epithelium
4. Pseudostratified columnar epithelium
5. Stratified squamous epithelium

**Key Points:** All epithelia have the following features:

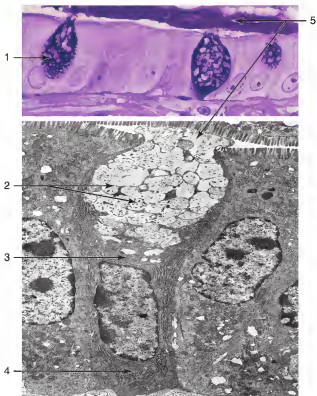
- One or more layers of cells held together by junctional complexes.
- The basal cell layer is held by **hemidesmosomes** to an extracellular **basal lamina** or basement membrane composed of **type IV collagen**, **laminin**, and other glycoproteins.
- Epithelial cells show **polarity**, with membrane proteins on their apical domains that are generally different from those on their basolateral domains.

Functions of epithelia depend on their structures:

- **Simple squamous epithelia**, with one layer of flattened cells (eg, the endothelium lining blood vessels), generally separate tissue compartments and allow selective transfer of material through their cells.
- **Simple cuboidal epithelia**, with one layer of roughly cube-shaped cells (eg, lining of many ducts from glands), have similar functions, but their additional cytoplasm allows more energy-dependent transfer of material as well as secretion of products from these cells.
- **Simple columnar epithelia**, with one layer of tall cells (eg, lining of the intestines and gallbladder), not only separate tissue compartments but allow extensive, energy-dependent uptake of material across the cell layer (absorption).
- **Pseudostratified columnar epithelia**, with a single cell layer on the basement membrane but containing cells of varying heights (eg, lining of upper respiratory tract), have functions of simple columnar epithelia but also contain various specialized cells.
- **Stratified squamous epithelia** (eg, epidermis) have multiple layers, with cells becoming keratinized and flattened as they move from the basal layer to apical layers. Such epithelia generally protect underlying cells from damage due to dehydration or friction.

**Clinical Note:** Certain changes between simple and stratified morphology in some epithelia, caused by environmental or other influences, may indicate precancerous changes in the cells.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 73-75.*



## GOBLET CELLS: UNICELLULAR MUCOUS GLANDS

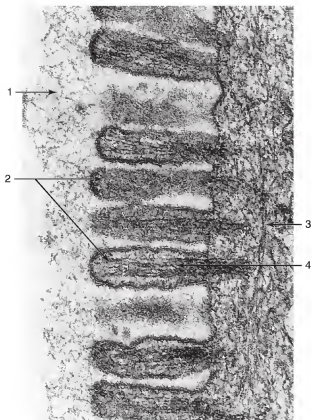
1. Goblet cell
2. Secretory granules with mucin
3. Golgi apparatus
4. Rough endoplasmic reticulum (RER)
5. Secreted mucus

**Key Points:** Goblet cells have the following characteristics:

- They can be found in either simple or pseudostratified columnar epithelia.
- They are tall cells, attached to basal lamina but with apical ends at the epithelial surface.
- In the basal portion, each has a nucleus surrounded by RER. Apical to this is a well-developed Golgi apparatus, above which the cell becomes greatly expanded and filled with large secretory granules.
- The granules contain glycoproteins called mucins, which are 80% oligosaccharide and 20% protein.
- Upon exocytosis, mucins become greatly hydrated and form a layer of mucus, which protects all the epithelial cells from abrasion and invasion by microorganisms.
- These cells are particularly abundant in the lining of the digestive and respiratory tracts.

**Clinical Note:** In **chronic bronchitis**, common among habitual smokers, the number of goblet cells in the lining of small bronchi and bronchioles often increases greatly. This leads to excessive mucus production in areas where there are too few ciliated epithelial cells for its removal and contributes to obstruction of these airways.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 76-77.*



## MICROVILLI AND GLYCOLALYX

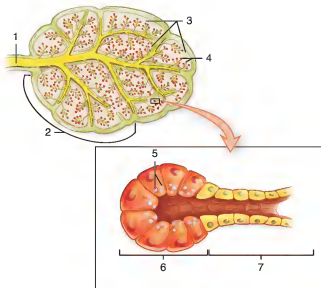
1. Glycocalyx or cell coat
2. Microvilli
3. Terminal web
4. Actin filaments

**Key Points:** Major features of **microvilli** include:

- They are small, finger-like projections from the apical surface of columnar or cuboidal epithelial cells.
- Each is typically cylindrical, about 1  $\mu\text{m}$  tall and 0.08  $\mu\text{m}$  in diameter.
- Generally the major function of microvilli is to increase the cells' apical surface area and facilitate absorption.
- The cell membrane of microvilli often includes a thick layer of oligosaccharides attached to membrane glycoproteins and forming the **glycocalyx** or cell coat.
- Internally, the core of each microvillus contains a loose bundle of parallel **actin filaments** with associated molecules of myosin I and fimbrin.
- At the base of each microvillus, the core actin filaments interact with a layer of similar filaments bound to underlying intermediate filaments. This layer of actin and intermediate filaments stains more heavily than neighboring cytoplasm and comprises the **terminal web** at the apical ends of cells with microvilli.

**Clinical Note:** **Celiac disease** is a disorder of the small intestine characterized by an abnormal immune response to antigens ingested with wheat or rye flour, commonly the protein gluten. Reactive T cells can damage the simple columnar epithelium lining the intestine, leading to loss or diminished function of the cell's apical microvilli. This causes generalized malabsorption in the small bowel and diarrhea.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 70-71.*





## GENERAL STRUCTURE OF EXOCRINE GLANDS

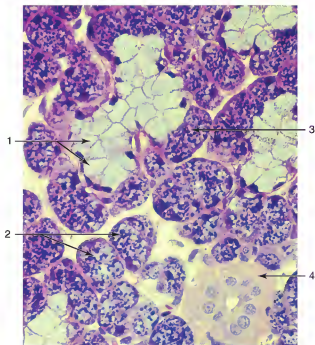
1. Duct draining gland
2. Lobe
3. Lobules
4. Secretory acini
5. Secretory vesicles
6. Acinus (secretory portion)
7. Duct (conducting portion)

**Key Points:** Exocrine glands have the following features:

- Contain secretory epithelia, which are continuous with the epithelium of at least one duct.
- Secretory portions of the gland may be rounded (**acini**) or elongated (**tubules**).
- Acini or tubules comprise the **parenchyma** or functional tissue of the gland; supportive connective tissue surrounding these components makes up the gland's **stroma**.
- Secretory cells are often shaped like blunt pyramids, with their nucleated basal ends on the basement membrane and the apical ends lining the lumen of the acinus.
- **Ducts** are usually simple cuboidal epithelia, surrounded by connective tissue.
- Small ducts from each acinus or tubule converge to make larger ducts, which drain the gland.
- **Vesicles** with product to be secreted form via the rough endoplasmic reticulum and Golgi apparatus and accumulate at the apical end of the cells.
- Secretion into the lumen for passage into the draining ducts occurs by one of three mechanisms:
  - **Merocrine secretion**, involving exocytosis
  - **Apocrine secretion**, involving detachment of apical portions of the cells, typically containing lipid droplets
  - **Holocrine secretion**, involving detachment and breakup of the entire cell filled with secretory product

**Clinical Note:** It is not uncommon for epithelial cells in glands to undergo neoplastic changes, producing benign growths called **adenomas** or malignant tumors called **adenocarcinomas**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 76-79.*



## TUBULOACINAR, SEROMUCOUS GLANDS

1. Mucous cells in secretory tubule
2. Serous cells in secretory acini
3. Serous demilune
4. Striated duct

**Key Points:** Cells in the secretory portions of exocrine glands generally produce either a mucus-rich secretion or a more watery, enzyme-rich secretion, which can be distinguished histologically:

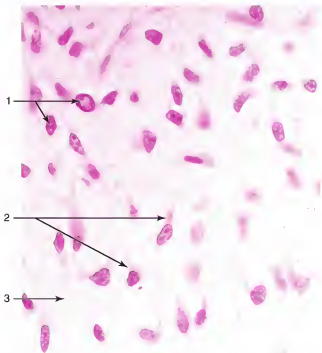
- **Mucous cells** stain poorly due to loss of the very water-soluble mucins during tissue preparation.
- Cells filled with vesicles of proenzymes stain well with many stains and are called **serous cells**.

Most exocrine glands have secretory portions that are either entirely serous or entirely mucous, but certain salivary glands, such as the sublingual gland shown in the figure, contain both **serous acini** and **mucous tubules**. The mucous cells can be seen to converge on very small lumens. The rounded clumps of serous cells at the ends of some mucous tubules are called **serous demilunes**.

The duct shown is a **striated duct**, with the basolateral domains of its cells folded into many deep invaginations. These are associated with many mitochondria, which are eosinophilic and cause the faint pink staining of the striations. Enzymes in such folds are involved in recovering ions secreted with the product of the serous and mucous cells.

**Clinical Note:** **Mumps** is an acute illness of childhood caused by a viral infection of cells in the major salivary glands (and other organs), leading to painful swelling of these exocrine glands.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 82.*



## MESENCHYME

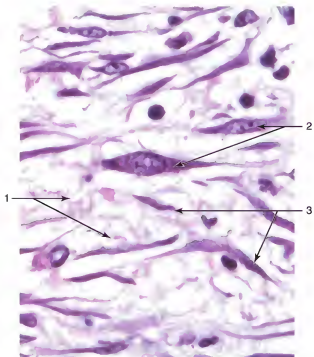
1. Nuclei of mesenchymal cells
2. Cytoplasm of mesenchymal cells
3. Ground substance

**Key Points:** Mesenchyme is a specialized type of developmentally important connective tissue with the following characteristics:

- Found between and supporting the developing organs of embryos and early fetuses.
- Contains almost exclusively undifferentiated, elongated cells with large oval nuclei and smaller, tapering cytoplasmic regions (**mesenchymal cells**).
- As in all connective tissues, the total volume of extracellular space exceeds the volume of the cells.
- The extracellular space is filled with hydrated “**ground substance**” containing glycosaminoglycans, mostly **hyaluronic acid**, and very fine collagen fibers.
- Cells are mostly derived from the middle embryonic layer (**mesoderm**), along with some migrating **neural crest cells** that formed during neural tube formation and stem cells of other tissues.
- Mesenchymal cells proliferate and differentiate to form most cells of connective tissues and muscles.

**Clinical Note:** Small regions of tissue resembling mesenchyme remain in certain adult organs, such as the pulp cavities of teeth and some adipose tissue. Investigators in the new field of **regenerative medicine** extract from such tissues multipotent mesenchymal cells that are potentially useful in grafts to replace damaged tissue in some patients.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 86-87.*



## FIBROBLASTS

1. Extracellular matrix
2. Active fibroblasts
3. Inactive fibroblasts

**Key Points:** Fibroblasts are the cells that produce collagen and most components of ground substance in all connective tissues. Connective tissues produced by fibroblasts make up the key supportive component or **stroma**, as well as the enclosing capsule and other organizing layers of every organ. Usually derived from mesenchymal cells, fibroblasts resemble such cells with elongated nuclei and tapering cytoplasm.

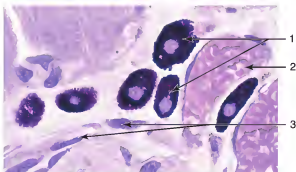
- Inactive fibroblasts have darker staining, less conspicuous nuclei, and little cytoplasm.
- Inactive fibroblasts are activated by polypeptide **growth factors** to become metabolically active and grow.
- Active fibroblasts are involved in **glycosaminoglycan (GAG)** synthesis and **collagen** production and, therefore, have enlarged, euchromatic nuclei with nucleoli and more abundant cytoplasm that is basophilic due to the presence of rough endoplasmic reticulum (RER).
- The abundant **extracellular matrix** surrounding all fibroblasts contains fibers of collagen as well as ground substance composed of GAGs.

Fibroblasts differ from mesenchymal cells in the following ways:

- Most fibroblasts are differentiated cells specialized for collagen and GAG production.
- Connective tissues containing fibroblasts have extracellular space filled primarily with collagen or ground substance containing some collagen, as well as wandering leukocytes from the blood, such as the rounded cells shown in the figure.

**Clinical Note:** Fibroblasts are key cells in the closure of wounds and tissue repair. Growth factors released from blood platelets and from local sources in injured tissues induce fibroblast proliferation. These cells then differentiate to produce collagen-rich **scar tissue**, which seals the wound and restores some degree of function of the injured organ.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 86-89.*



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## MAST CELLS

1. Mast cells with cytoplasmic granules
2. Venule
3. Fibroblasts
4. Collagen
5. Secretory granules of mast cell
6. "Scroll-like" ultrastructure of some mast cell granules

**Key Points:** Mast cells are large round or oval cells, filled with highly basophilic secretory granules, which are found near venules and other small blood vessels in many connective tissues. Although inconspicuous with hematoxylin and eosin (H&E) staining, mast cells have the following features:

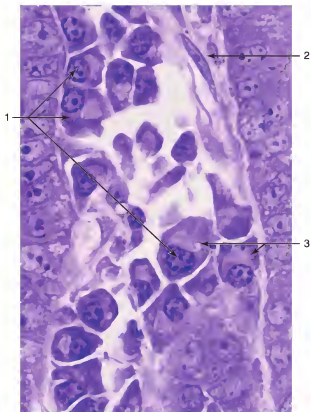
- Cytoplasm is packed with **heterogeneous secretory granules**, with diameters ranging from 0.3 to 2.0  $\mu\text{m}$ .
- Granule contents cause a change in color with some stains, a phenomenon called **metachromasia**.
- Ultrastructurally, some granules show internal scroll-like structures, the significance of which is not clear but which are characteristic of mast cells.

Mast cells are important cells in various local immune reactions. Upon stimulation, granules of mast cells undergo exocytosis and release many factors, including:

- **Histamine**, a low molecular weight substance that stimulates smooth muscle contraction, increased vascular permeability, and various effects in other tissues
- **Heparin**, a sulfated GAG with anticoagulant properties
- Several other substances including **chemotactic factors** and **leukotrienes** that mediate various aspects of inflammation, allergies, and immune defense

**Clinical Note:** Factors released from mast cells are responsible for many common local responses to external allergens such as pollen and bee stings. Collectively, mast cell factors induce events of the **immediate hypersensitivity reaction**, which include itching, redness, sneezing, mucus and tear production, and other characteristic local responses to foreign material.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 90-92.*



## PLASMA CELLS

1. Plasma cells
2. Endothelial cell
3. Golgi apparatus enlarged for immunoglobulin glycosylation

**Key Points:** Plasma cells are oval cells that differentiate from activated, clonally produced B lymphocytes. Plasma cells secrete immunoglobulins, typically after leaving the lymphatic vasculature for connective tissue spaces. They are very abundant in lymph nodes but can be found in connective tissue throughout the body.

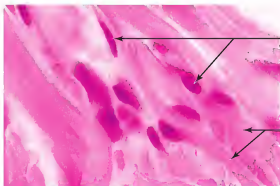
Characteristic features include:

- Round, euchromatic nuclei with small clumps of peripheral heterochromatin
- Basophilic cytoplasm
- Large, well-developed perinuclear Golgi complexes

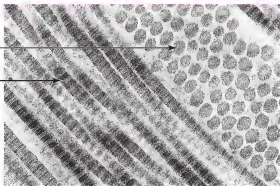
The Golgi complex is the site of glycosylation of the glycoproteins that make up the immunoglobulins, or antibodies. As the major cells for antibody synthesis, plasma cells are important parts of the adaptive immune system.

**Clinical Note:** Multiple myeloma is the most common neoplasm arising from plasma cells and is characterized by many separated sites of malignant plasma cell infiltration into bone marrow.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 93.*



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## COLLAGEN TYPE I

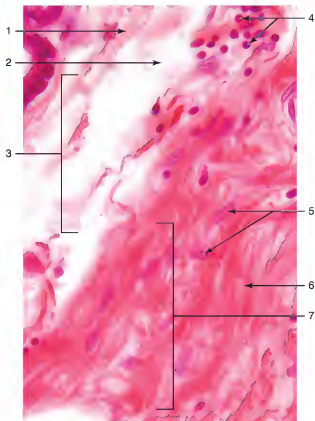
1. Fibroblasts
2. Bundles of collagen I fibrils in dense irregular connective tissue
3. Collagen I fibril cut transversely
4. Collagen I fibril cut longitudinally

**Key Points:** Collagen I is the most abundant type of collagen in the body and is found in all connective tissue proper and in bone. Usually produced by **fibroblasts**, collagen I forms 300-nm diameter fibrils, which often aggregate further as large eosinophilic bundles. Fibrils of collagen I have great tensile strength and provide collagen-rich tissues with toughness and durability. Important aspects of collagen synthesis include the following:

- Synthesis in RER of **procollagen  $\alpha$  chains**, in which every third amino acid is glycine, with the remainder rich in proline and lysine.
- Specific **prolines and lysines are hydroxylated**, in processes requiring vitamin C.
- Specific hydroxylysines are **glycosylated**.
- The modified procollagen  $\alpha$  chains now form **triple helices** in the endoplasmic reticulum (ER) cisternae, with nonhelical **terminal propeptides** keeping the procollagen complex soluble.
- In the Golgi apparatus, the procollagen is packaged into **secretory vesicles**.
- After exocytosis, the **terminal propeptides are cleaved** by extracellular peptidases, and the **complexes aggregate into the 300-nm collagen fibrils**, with the regular, evenly spaced assembly of the collagen fibrils indicated by the cross-striations visible by transmission electron microscopy (TEM).
- The fibrillar structure is reinforced by **covalent cross-links** formed between the collagen complexes.

**Clinical Note:** Diets chronically deficient in vitamin C (ascorbic acid) can lead to inadequate hydroxylation of procollagen protein by enzymes of the RER and failure to produce normally assembled collagen fibrils. This condition is called **scurvy** and is often first manifested by loosening of teeth. Vitamin C, along with  $O_2$  and  $Fe^{2+}$ , is a cofactor for the enzyme proline hydroxylase.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 94-98.*



## LOOSE AND DENSE IRREGULAR CONNECTIVE TISSUE

1. Sparse collagen I bundles
2. Ground substance
3. Loose connective tissue
4. Wandering leukocytes
5. Fibroblasts
6. Dense collagen I bundles
7. Dense irregular connective tissue

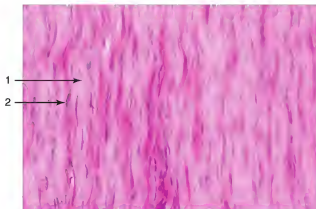
**Key Points:** Two major types of “connective tissue proper” are termed loose and dense irregular. Both are derived from embryonic mesenchyme and are formed by the synthetic activity of fibroblasts. Both types are found in the dermis of skin and in the capsules of many organs. These types of connective tissue constitute the parts of organs through which most small blood vessels run.

**Loose connective tissue** contains approximately equally sized areas of sparse collagen bundles and ground substance rich in hydrated GAGs. Fibers of elastin and reticulin (collagen III) are also normally present. All of the extracellular material is secreted from the scattered fibroblasts. Various kinds of leukocytes, particularly lymphocytes, are normally also present in such tissue, along with variable numbers of adipocytes. Loose connective tissue is also called **areolar tissue**.

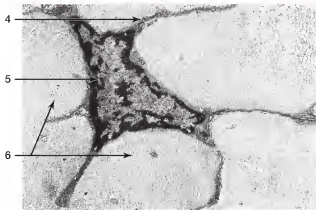
**Dense irregular connective tissue** is similar to the loose type with which it is commonly found, but contains a much greater density of collagen and much less ground substance. Fibroblasts are typically more numerous in dense connective tissue.

**Clinical Note:** **Scleroderma** is a rare but progressive disorder caused by excess collagen in dense irregular connective tissue, which hardens and tightens the affected organs. It can be localized to the dermis of the skin but can also involve connective tissue of internal organs. The fundamental cause is unknown, but autoimmunity is involved, producing chronic inflammation and excessive collagen synthesis by fibroblasts.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 104-106.*



3 Shown above is a section of \_\_\_\_\_.





## DENSE REGULAR CONNECTIVE TISSUE

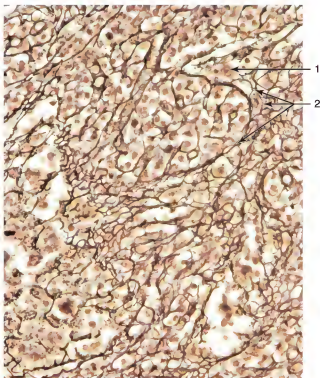
1. Dense collagen I bundles
2. Fibroblast
3. Dense regular connective tissue
4. Cytoplasm of fibroblast
5. Nucleus of fibroblast
6. Parallel collagen I bundles cut transversely

### Key Points:

- In dense regular connective tissue, such as tendons and ligaments, parallel bundles of collagen I are packed together, with numerous fibroblasts wedged among the bundles.
- This arrangement of collagen and the lack of ground substance produce a tissue with extremely high tensile strength.
- Leukocytes and other cells, as well as most blood vessels, are normally absent from dense regular connective tissue.

**Clinical Note:** Overuse of tendon-muscle units can frequently result in **tendonitis**, characterized by inflammation of the tendons and their attachments to muscle. Common locations are the elbow, the Achilles tendon of the heel, and the shoulder rotator cuff. The localized inflammation produces pain and swelling, which restrict the affected area's normal range of motion. The inflammation can be relieved by cortisone injection or treatment with other anti-inflammatory agents, after which the fibroblasts repair any damage to the collagen bundles.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 106-108.*



3. What tissue type is this?

## RETICULAR CONNECTIVE TISSUE

1. Reticular cells
2. Reticular fibers
3. Reticular tissue

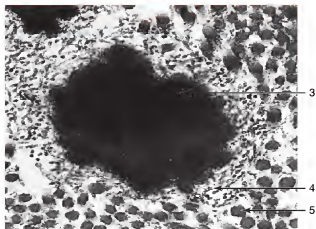
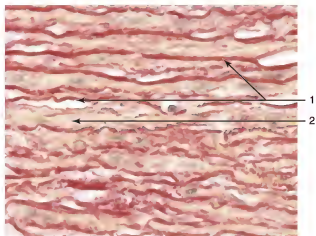
### Key points:

- Reticular connective tissue has an extracellular matrix containing mainly thin fibers of **collagen III**, also called **reticulin**.
- These fibers are heavily glycosylated, which makes them **argyrophilic**, allowing them to be **stained black** in special stains containing silver salts and without which they are hard to identify.
- Reticular tissue contains modified fibroblasts called **reticular cells**, which produce the collagen III.
- Reticular tissue is particularly abundant in lymphoid organs (spleen, bone marrow, lymph nodes), where the reticulin fibers provide a framework for attachment of lymphocytes and other cells, some of which can be seen in the figure.

Networks of reticulin are also found in the extensible areas of connective tissue in areas such as the dermis, lung, and blood vessels. In such locations, collagen I is also present.

**Clinical Note:** Mutations in the gene for the procollagen III  $\alpha$  chain produce a rare disorder called Ehlers-Danlos type 4 syndrome. Affected individuals have skin that is more transparent and thinner than normal and bruise easily due to fragile microvasculature. The disorder is a serious medical problem because the walls of large vessels are also weaker and liable to rupture. Surprisingly, given the prominence of collagen III in lymphoid tissues, abnormalities of immune function have not been reported for these patients.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 108.*



## ELASTIC FIBERS

1. Elastic fibers or sheets
2. Smooth muscle fiber
3. Elastin of developing fiber, cut transversely
4. Fibrillin microfibrils around elastin
5. Collagen type I fibers cut transversely

**Key Points:** Elastic fibers or sheets (lamellae) are assembled in the extracellular matrix from secreted components, usually from fibroblasts or smooth muscle cells. They provide tissues rich in this material with greater elasticity, flexibility, and distensibility.

Synthesis involves:

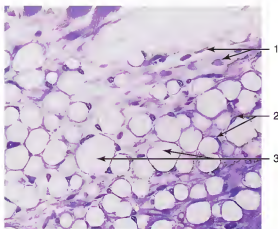
- secretion of the glycoprotein **fibrillin** and its assembly into microfibrils;
- secretion of the elastin subunits, sometimes called **tropoelastin**, and their association with fibrillin; and
- covalent cross-linking of the subunits into the larger fibers or sheets, which are capable of stretching.

Unlike collagen synthesis, in which the subunits are arranged like the parallel strands in a cable to form a very strong structure, elastin synthesis involves subunits arranged and bound together like a knotted mass of rubber bands, to form a strong but very elastic structure.

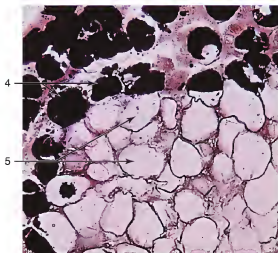
Elastic fibers are found in many examples of connective tissue proper, but usually require special stains to be seen readily. They are abundant in the dermis, mesenteries, layers of the digestive tract, and walls of large blood vessels. Large elastic arteries such as the aorta contain elastic sheets between thin layers of smooth muscle and surrounding both sides of the muscular layer. Distension or stretching of these sheets when blood is pumped into such vessels helps propel blood further along as the sheets rebound to their normal size.

**Clinical Note:** In **Marfan syndrome**, caused by mutations in the gene for fibrillin-1, connective tissues with abundant elastic fibers have abnormal elasticity, which leads to structural and functional defects in the skeletal, respiratory, cardiovascular, and other systems.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 98-100.*



6



## WHITE ADIPOSE TISSUE

1. Fibroblasts
2. Nuclei of adipocytes
3. Area of lipid droplet in adipocytes
4. Lipid droplet fixed and stained with osmium
5. Empty areas where lipid was unfixed and removed

**Key Points:** Adipose tissue is loose connective tissue that also contains a great number of cells specialized for fat storage called **adipocytes**. The cytoplasm of each adipocyte in white adipose tissue consists almost solely of a **single** or **unilocular lipid droplet**. This large inclusion of lipid pushes the nucleus and other organelles of the cell against the cell membrane. With most fixatives, lipid is not preserved and dissolves away when tissue sections are processed. Fixatives containing osmium tetroxide preserve lipid and stain the cytoplasmic droplets black.

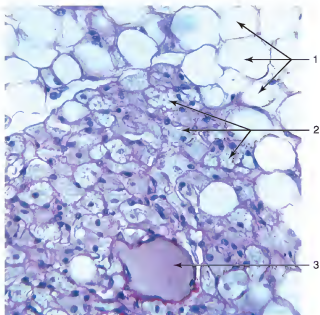
**White adipose tissue** normally makes up 15 to 25% of body weight and its functions include the following:

- Adipocytes store large amounts of very **energy-rich triglycerides** or neutral fats for use when dietary intake of nutrients is limited.
- Adipocytes secrete polypeptide hormones, such as **leptin**, which targets cells in the hypothalamus and elsewhere and helps regulate appetite, metabolism, and body mass.
- Adipose tissue **insulates** the body against rapid heat loss.
- Adipose tissue **cushions** internal organs and pads extremities such as the palms and soles.

Mobilization of triglycerides and release of fatty acids from adipocytes is triggered primarily by autonomic innervation of the cells and various hormones, such as glucagon.

**Clinical Note:** Excessive formation of adipose tissue, or **obesity**, occurs when energy intake exceeds energy expenditure. Although fat cells can differentiate from mesenchymal stem cells throughout life, **adult-onset obesity** is generally believed to involve primarily increased size (hypertrophy) in existing adipocytes. **Childhood obesity** can involve increased adipocyte size as well as formation of new adipocytes by proliferation (hyperplasia) of pre-adipocytes from mesenchymal cells. This increase in the number of adipocytes early in life may predispose an individual to obesity in later life.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 109-112.*





## BROWN ADIPOSE TISSUE

1. Adipocytes of white adipose tissue
2. Adipocytes of brown adipose tissue
3. Venule containing blood

**Key Points:** Brown adipose tissue of humans is found primarily in **neonatal infants**, with much involution and more restricted distribution in the upper chest and neck after early childhood. Adipocytes of this tissue function principally to generate heat that is transferred to the blood, warming the body in a process of **nonshivering thermogenesis**.

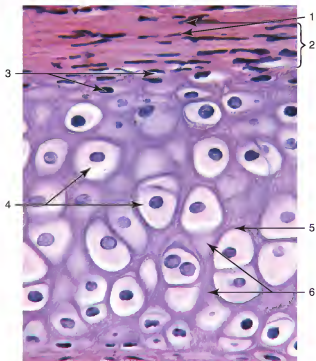
Adipocytes of brown adipose tissue have the following features:

- Many **small multilocular lipid droplets** are evenly distributed throughout the cytoplasm.
- The nucleus and other organelles are dispersed in the cytoplasm among the small lipid droplets.
- **Abundant mitochondria**, along with a **rich vascular supply**, give the tissue its brown appearance.
- As stored triglycerides are broken down in the mitochondria, the mitochondrial inner membrane protein **thermogenin**, or **uncoupling protein**, uncouples the released energy from ATP formation, allowing it to be dissipated as heat, which warms blood in the adjacent microvasculature.

Brown adipose tissue is more abundant in mammals that hibernate in cold weather.

**Clinical Note:** Benign tumors of adipose tissue, called **lipomas**, are fairly common. Brown adipose tissue that does not undergo involution may continue to grow in adults and produce benign tumors that are denoted as **hibernomas**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 112-113.*



7

## HYALINE CARTILAGE

1. Fibroblasts
2. Perichondrium
3. Chondroblasts
4. Chondrocytes in lacunae
5. Pericellular condensation of matrix
6. Matrix

### Key Points: Hyaline cartilage:

- is the most common and abundant form of cartilage in adults and forms the temporary skeleton in the embryo before being replaced by bone;
- is translucent and bluish-white in the fresh state;
- is usually surrounded by **perichondrium** containing dense connective tissue and stem cells called **chondroblasts**;
- and, inside the perichondrium, has much extracellular matrix and postmitotic **chondrocytes**, each contained within a **lacuna**.

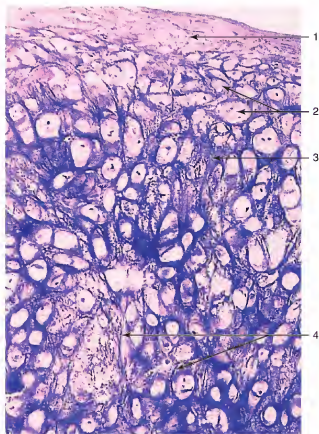
The abundant matrix around the lacunae is composed primarily of **collagen type II** and large **proteoglycan aggregates**, which have much bound water and attach to polymers of **hyaluronic acid**. Properties of the matrix make hyaline cartilage strong but somewhat flexible. Matrix is secreted by the chondrocytes and accumulates between the lacunae. A greater density of newly synthesized components immediately around a lacuna makes that **pericellular matrix** more darkly stained than matrix farther from lacunae.

Like other types of cartilage, hyaline cartilage has **no microvasculature**, and its cells rely on diffusion from capillaries in the perichondrium for  $O_2$  and nutrients, which restricts the size and thickness this tissue can achieve.

Chondroblasts newly surrounded by matrix may still divide one or two times, forming **isogenous aggregates** (clones of cells) in the same lacuna. As these cells secrete matrix, they isolate themselves into separate lacunae.

**Clinical Note:** Partly because it is avascular, hyaline cartilage has **limited capacity for repair** after injury. Repair cartilage forms very slowly from perichondrial cells and is usually much more fibrous than normal hyaline cartilage, containing collagen type I in addition to collagen type II.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 114-116.*



## ELASTIC CARTILAGE

1. Perichondrium
2. Chondrocytes in lacunae
3. Matrix
4. Elastic fibers in matrix

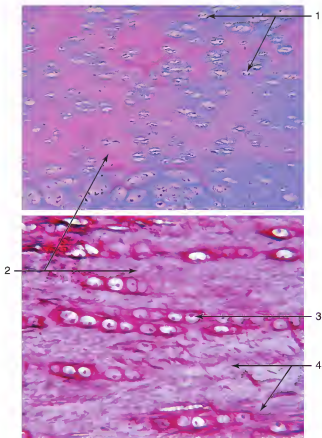
**Key Points:** Elastic cartilage is surrounded by **perichondrium** and is similar to hyaline cartilage in most respects but contains an abundant network of branching **elastic fibers** in addition to **collagen type II**. This gives it a yellowish color in the fresh state and causes the matrix to stain more darkly with most stains. Many stains reveal the bundles of elastic fibers.

Elastic cartilage is highly flexible, avascular, and occurs in:

- the external ear (auricle);
- the epiglottis; and
- the auditory (eustachian) tubes.

**Clinical Note:** Medical problems specifically associated with elastic cartilage are rare, even in patients with Marfan syndrome, in whom the fibrillin associated with elastin fibers is abnormal due to gene mutations. One exception is the formation of endochondral **pseudocysts** and softening (**chondromalacia**) of elastic cartilage in the auricle, which occur infrequently as a benign, painless swelling on the upper portion of the ear.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 116-118.*



## FIBROCARILAGE

1. Chondrocytes in lacunae
2. Matrix
3. Aligned lacunae of chondrocytes
4. Parallel and irregular bundles of collagen type I

**Key Points:** Fibrocartilage is a tissue intermediate between hyaline cartilage and dense connective tissue, containing elements of both. It is found primarily in the intervertebral disks and pubic symphysis, with smaller amounts in certain other joints and some attachment sites of tendon to bone.

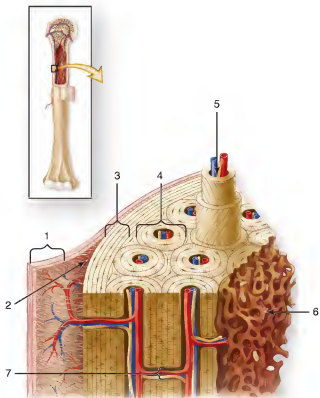
Fibrocartilage contains:

- individual and isogenous groups of **chondrocytes, often aligned**, in a matrix containing collagen type II and proteoglycans;
- **bundles of collagen** type I, generally parallel with some irregular dispersal, and scattered **fibroblasts**; and
- **no perichondrium**.

Like all cartilage, fibrocartilage is avascular, and its combination of matrix elements makes it both extremely strong and resistant to compression.

**Clinical Note:** With high levels of collagen in both its hyaline cartilage and fibrous components, fibrocartilage is weakened by genetic or dietary problems that lead to deficient or defective production of collagen. Fibrocartilage associated with ligaments of some mobile joints, such as the wrist, can undergo **peripheral tears** and other traumatic damage, particularly when weakened by defective collagen.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 118-120.*





## BONE ORGANIZATION

1. Periosteum
2. Perforating (Sharpey's) fibers
3. External circumferential lamellae
4. Osteon
5. Central (Haversian) canal of osteon
6. Trabeculae of spongy bone
7. Perforating (Volkmann) canal

**Key Points:** **Compact bone** is organized into many thin layers or **lamellae**. Its surface is covered by the **periosteum**, consisting of dense connective tissue overlying a more cellular layer with bone-forming osteoblasts. From the periosteum, **perforating (Sharpey's) fibers** penetrate the **external circumferential lamellae** of bone, firmly holding it in place. Most of the compact bone is organized as multiple **osteons**, which have the following parts:

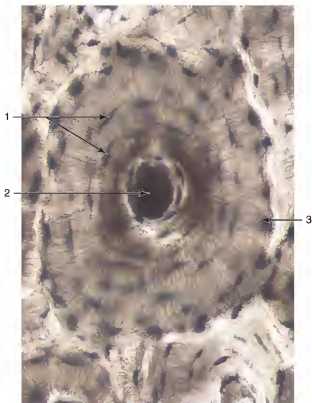
- a **central (Haversian) canal** containing an arteriole and a venule;
- several layers of **bone matrix** formed by osteoblasts;
- **osteocytes** located individually in **lacunae** between successive lamellae;
- small **canaliculi** extending from the lacunae and contacting those of neighboring lacunae.

As indicated diagrammatically in the figure, collagen fibers in the matrix of successive lamellae in an osteon are oriented in different directions, an arrangement that contributes to the great strength of bone. The blood vessels in parallel osteons may be connected in short **perforating (or Volkmann) canals**.

**Spongy or cancellous bone** typically surrounds the internal marrow cavities of bones and consists of many small trabeculae or spicules of bone. Trabeculae of spongy bone are usually covered by a delicate layer of connective tissue called **endosteum**.

**Clinical Note:** When a bone is broken, macrophages clean up the injured site, and periosteal cells and capillaries grow into the area. Collagen formation first produces a loose connective tissue, which then becomes dense with developing areas of hyaline cartilage. This new **callus** stabilizes the bone and is gradually replaced by a **bony callus**. The underlying broken bone, along with the callus, is slowly remodeled over the next several weeks into new compact lamellar bone.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 121-125.*



## OSTEON

1. Lacunae
2. Central (Haversian) canal
3. Canaliculi crossing a lamella

**Key Points:** In ground preparations of bone, which are not decalcified, **osteons** of compact bone have empty **central canals** and **lacunae**, the blood vessels and osteocytes having been lost during tissue preparation. Concentric lamellae closest to the central canal are those most recently formed by osteoblast activity and are thinner. Fine **canaliculi** extend from each lacuna, crossing the lamellae and connecting adjacent lacunae. This arrangement of canaliculi allows diffusion of nutrients and wastes between all the osteocytes in the lacunae and the vasculature in the central canal. Collagen bundles in the bony matrix around the canaliculi provide strength to the bone.

An osteon is formed in a process that involves the following:

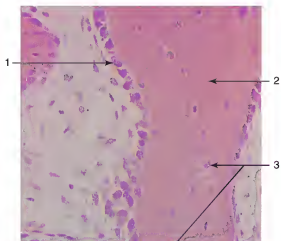
- Osteoblasts lining an excavated tunnel of bone secrete a lamella (layer) of **osteoid**, which surrounds long cytoplasmic processes extending from the cells and the osteoid calcifies.
- After a pause, osteoblasts produce another layer of osteoid, but some osteoblasts remain in flattened **lacunae** between the two lamellae.
- As the osteoid is calcified, osteoblasts in lacunae differentiate into nondividing **osteocytes**, with the cytoplasmic processes in the small **canaliculi** crossing the lamellae.
- Successive waves of osteoblast secretion produce the series of concentric lamellae, with lacunae interconnected by the canaliculi.

Osteocytes remain enclosed within lacunae and help maintain the surrounding bony matrix. They are in contact via gap junctions along their cytoplasmic processes. Osteocytes are important in controlling daily fluctuations in blood calcium and phosphorus.

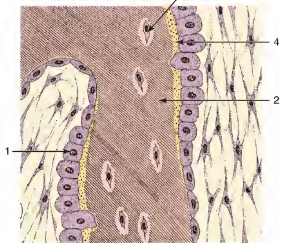
Osteons are temporary structures, being demolished periodically as bone is broken down by osteoclasts and replaced by the formation of new osteons. Such bone remodeling allows the new bone to accommodate new stresses, such as those caused by bodily growth, obesity, and changes in activity.

**Clinical Note:** Osteocytes also act as mechanical sensors, monitoring areas within bones where mechanical loading has been increased or decreased and maintaining the adjacent matrix accordingly. **Lack of exercise** or the **weightlessness** experienced by astronauts leads to decreased bone density.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 128.*



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## OSTEOBLASTS AND OSTEOCYTES

1. Osteoblasts
2. Bone matrix
3. Osteocytes in lacunae
4. Osteoid

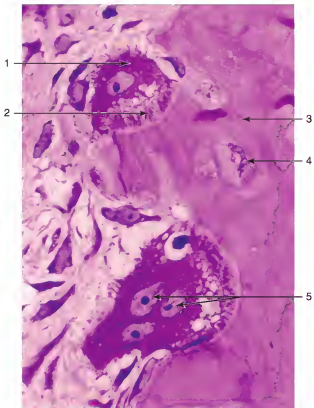
**Key Points:** Osteoblasts are typically found as a single layer on the surfaces of developing bone, covered in turn by mesenchyme, periosteum, or endosteum. Osteoblasts divide slowly and then begin to secrete **osteoid**, containing much collagen type I, which constitutes 90% of bone protein, various glycoproteins and proteoglycans, and components that promote calcification. The calcification process includes the following steps:

- Osteonectin and various other proteins in osteoid bind calcium, raising local concentrations of this ion.
- Matrix vesicles released from osteoblasts contain alkaline phosphatases, which increase the local concentration of phosphate ions.
- High levels of calcium and phosphate ions locally within osteoid lead to the formation of  $\text{CaPO}_4$  crystals around the matrix vesicles.
- These then initiate gradual mineralization via the deposition of calcium hydroxyapatite throughout the osteoid, converting it to more the acidophilic **bone matrix**.

Osteoblasts trapped within lacunae and surrounded by matrix no longer divide and differentiate as **osteocytes**, which maintain the matrix and release calcium and phosphate from the surrounding matrix as needed elsewhere in the body.

**Clinical Note:** Osteogenesis imperfecta is a group of related diseases resulting from deficient production of collagen type I or synthesis of defective collagen components by osteoblasts. Such defects lead to a spectrum of disorders, all characterized by significant fragility of the bones.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 121-124.*



## OSTEOCLASTS

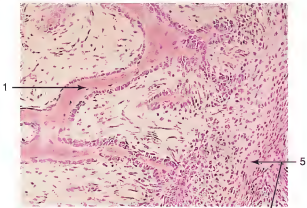
1. Osteoclast
2. Ruffled border of osteoclast
3. Bone matrix
4. Osteocyte
5. Multiple nuclei of an osteoclast

**Key Points:** Osteoclasts have the following features:

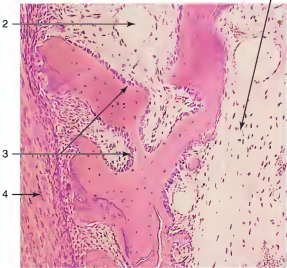
- They are very **large** cells with **multiple nuclei**.
- They are formed in bone by the fusion of several **monocytes** from the blood.
- They are responsible for major bone resorption and are often located within shallow **resorption bays** (or Howship's lacunae) on bony surfaces.
- Into this bony depression, the osteoclast extends many processes, comprising the "**ruffled border**" at which the cell adheres tightly to the bone.
- From its ruffled border, the cell secretes **collagenases** and other degradative enzymes and pumps ions that produce an **acidic microenvironment** in the resorption bay.
- Together these components dissolve the bony matrix.
- They are target cells for the thyroid polypeptide **calcitonin**, which decreases their activity.

**Clinical Note:** Paget disease, or **osteitis deformans**, is a chronic disorder characterized by excessive activity of osteoclasts, followed by increased activity of osteoblasts. The aberrant activity of these cells leads to formation of weak, deformed compact bone and excessive cancellous or spongy bone.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 125-127.*



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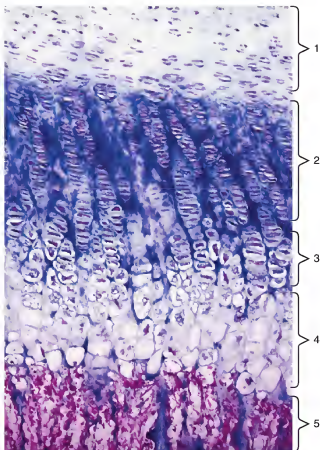
## INTRAMEMBRANOUS OSSIFICATION

1. Bone matrix
2. Blood vessel
3. Osteoblasts
4. Periosteum
5. Mesenchyme

**Key Points:** Intramembranous ossification, named because it occurs within fetal “membranes” of condensed mesenchyme, is the process that forms most flat bones of the skull and jaws. It begins when **mesenchymal cells** in several areas differentiate as **osteoblasts** and secrete **osteoid**, which undergoes calcification to form an **ossification center**. Growth of these areas leads to their eventual fusion to form two thin layers of compact bone, the internal and external tables or plates of the completed skull and jaw bones. Between these plates lies an area called the **diploë** consisting of spongy bone and marrow. The outer surfaces of the forming bony plates are covered by mesenchyme that develops into **periosteum**.

**Clinical Note:** Cleidocranial dysplasia is a rare congenital disorder that stems from defects in a transcription factor needed for the differentiation of osteoblasts, particularly those involved in intramembranous ossification. It is characterized by delayed or incomplete closure of the fontanelles between bones of the skull and by defects of the palate and jaws.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 129.*



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## ENDOCHONDRAL OSSIFICATION

1. Zone of resting cartilage
2. Zone of proliferating cartilage
3. Zone of hypertrophic cartilage
4. Zone of calcified cartilage
5. Zone of ossification

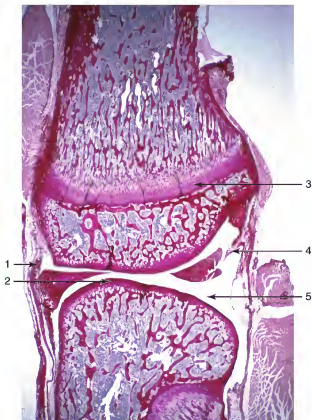
**Key Points:** In **endochondral ossification** components of the embryonic skeleton composed of **hyaline cartilage** grow and are replaced by bone. The perichondrium is converted locally to periosteum, with osteoblasts producing a **bony collar**, usually first around the diaphysis. Chondrocytes in the cartilage surrounded by this collar hypertrophy die, creating spaces into which migrating osteoprogenitor cells and capillaries enter from the periosteum to establish the **primary ossification center**. Slightly later, **secondary ossification centers** form similarly in the cartilage at the epiphyses of developing long bones.

Between these two ossification centers, a narrow region of hyaline cartilage is established as part of the **epiphyseal growth plate**, which allows continuous growth and elongation of bones until adulthood, when it disappears. This growth plate in endochondral ossification is usually considered as an interrelated series of developing zones, which from the epiphysis to the diaphysis include:

- the zone of “**resting**” **epiphyseal hyaline cartilage**;
- a zone in which **chondrocytes begin to proliferate**, forming stacks of cells within long lacunae;
- a zone in which these **chondrocytes swell (hypertrophy)**, compressing the matrix into thin septa between enlarged lacunae;
- a zone in which these **chondrocytes die**, creating spaces and allowing **calcification of the matrix** to begin; and
- a broader zone where this new calcified matrix is invaded by capillaries and osteoblasts from the primary (diaphyseal) ossification center and undergoes **ossification of new bone** continuous with that in the diaphysis.

**Clinical Note:** Chondrocyte proliferation in the growth plate during childhood depends on growth hormone (GH) from the pituitary. Deficiency of GH can lead to **dwarfism**, whereas excess GH can cause **gigantism**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 129-131.*



## SYNOVIAL JOINT (DIARTHROSIS)

1. Joint capsule
2. Articular cartilage
3. Epiphyseal cartilage of growth plate
4. Synovial membrane
5. Joint cavity

**Key Points:** Diarthroses, or synovial joints, move freely and generally have these components:

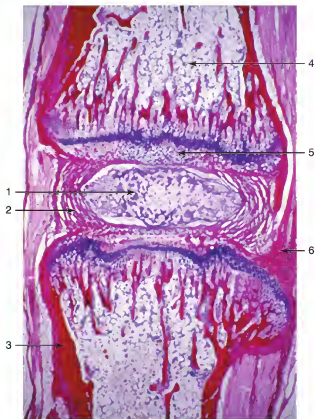
- a dense connective tissue **capsule**, continuous with the ligaments between the bones;
- a **cavity** filled with lubricant **synovial fluid** bathing internal components of the joint; and
- thin layers of **articular cartilage** that resemble hyaline cartilage without periosteum and form a protective cover on each epiphysis of the bones involved.
- In young people a growth plate containing **epiphyseal cartilage** that disappears when adult size is reached
- **Synovial membrane**, a specialized connective tissue rich in fenestrated capillaries that lines and projects inwardly from the capsule.

The synovial membrane contains two cell types important for function of the joint:

- **phagocytic synovial cells**, derived from monocytes and located near the surface of the membrane to remove tissue debris from the synovial fluid; and
- **secretory synovial cells**, derived from mesenchyme, which produce much **hyaluronic acid** and other glycosaminoglycans. These components and plasma from the capillaries makes up the synovial fluid

**Clinical Note:** In **rheumatoid arthritis**, chronic inflammation of the synovial membrane causes thickening of this connective tissue and stimulates the macrophages to release collagenases and other hydrolytic enzymes. Such enzymes eventually cause destruction of the articular cartilage, allowing direct contact of the bones within the joint.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 134-137.*



## INTERVERTEBRAL DISK

1. Nucleus pulposus
2. Annulus fibrosus
3. Periosteum and bone
4. Bone marrow
5. Articular cartilage of vertebra
6. Dense connective tissue of ligament

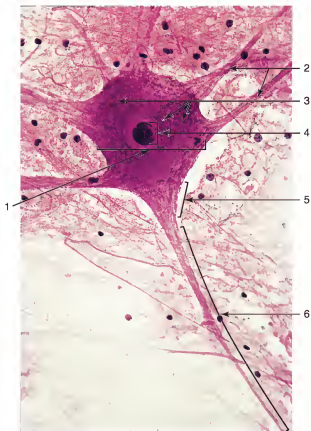
**Key Points:** Vertebrae of the spinal column are separated by thick disks of fibrocartilage that lie between the articular cartilage covering each bony vertebra and are held in place by ligaments. In each **intervertebral disk**, the fibrocartilage forms two components:

- a central **nucleus pulposus** containing a gel-like matrix rich in hyaluronate and fluid, which allow the disk to cushion forces acting on the vertebral column; and
- a peripheral **annulus fibrosis** surrounding the nucleus pulposus and consisting of multiple layers of dense regular connective tissue with bundles of collagen type I, which strengthen the disk structure.

These features allow these disks to act as protective shock absorbers between the vertebrae and provide strong, flexible support for the spinal column.

**Clinical Note:** Degenerative changes in fibrocartilage can result in weakness and tearing of the annulus fibrosus of an intervertebral disk, usually on the posterior side of a disk in the lumbar or lumbosacral region. This can allow the nucleus pulposus to herniate and compress the adjacent spinal nerves. Such **herniated or slipped intervertebral disks** can produce pain, numbness, and muscle spasms.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 137-139.*





## NEURON STRUCTURE

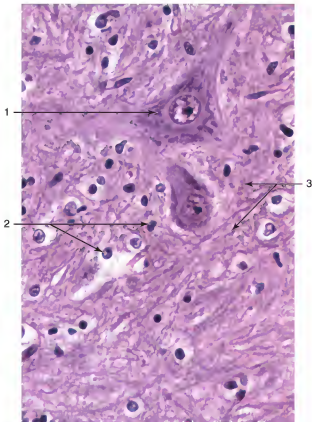
1. Cell body or perikaryon
2. Dendrites
3. Chromatophilic (Nissl) substance
4. Nucleus
5. Axon hillock
6. Axon

**Key Points:** Important parts of every neuron include:

- The large **cell body**, or **perikaryon**, receives stimuli from other neurons and serves as the **trophic center** for the neuron, synthesizing most cellular components.
- The **nucleus** within the cell body is usually large, rather spherical, and **euchromatic** (mostly pale staining), and often has a prominent **nucleolus**.
- **Rough endoplasmic reticulum (RER)** and **free polyribosomes** appear as basophilic material in the perikaryon termed **chromatophilic (Nissl) substance**, which reflects the neuron's synthetic state.
- One or many short, branching **dendrites** radiate from the perikaryon, serving as sites for large numbers of **synapses** and greatly increasing the **receptive area** of the neuron.
- Usually a single, very long **axon** (sometimes with branches called **collaterals**) extends from the perikaryon, for **impulse transmission** to other neurons or effector organs.
- Axons arise from pyramid-shaped regions of perikarya called **axon hillocks**, which are rich in ion channels involved in **generating action potentials** or nerve impulses.

**Clinical Note:** Hundreds of specialized neuronal types comprise the central and peripheral nervous systems, and the death or loss of normal function of specific neurons is characteristic of some neurological disorders. Neuronal death in a brain region called the substantia nigra leads to the muscle weakness and tremors of **Parkinson disease**. A genetic malfunction within neurons of the striate nucleus can cause **Huntington disease**, with movement disorders and dementia resulting from the intracellular accumulation of the huntingtin protein and death of the neurons involved.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 141-144.*



## NEURONS AND GLIAL CELLS

1. Neuronal cell body
2. Glial cells
3. Neuropil

**Key Points:** All **neurons** exist in intimate association with a surrounding network of **glial cells** which are much more numerous than neurons and support the neurons in many different ways. Glial cells are smaller than most typical neuronal perikarya and extend cytoplasmic processes related to their functions. Except around the larger blood vessels, the central nervous system (CNS) essentially lacks connective tissue. Instead, glial cells form the specialized neuronal microenvironment in which neuronal activity can occur. The dense network of dendrites, axons, and various glial cell processes makes up the **neuropil** and fills most of the spaces between the cell bodies within CNS tissue. The fibrous appearance of neuropil is due to these processes and is best seen with specialized stains.

Four major types of glial cells in the CNS are:

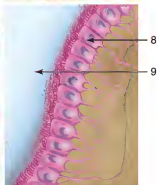
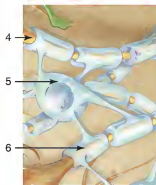
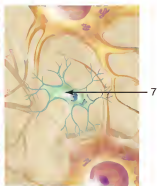
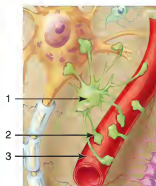
- **Astrocytes**
- **Oligodendrocytes**
- **Ependymal cells**
- **Microglial cells**

The numerous small glial cells with dark-staining nuclei seen in the figure are **astrocytes**, and the larger glial cells with more euchromatic nuclei and very pale cytoplasm are **oligodendrocytes**.

**Clinical Note:** The most common form of dementia in the elderly, **Alzheimer's disease**, affects neuronal perikarya and synapses of the cerebral cortex and some subcortical areas. In this disorder, functional defects within the neurons produce two characteristic pathological features:

- **Neurofibrillary tangles**, which involve microtubules and other parts of the cytoskeleton filling the perikarya and proximal processes
- **Neuritic plaques**, with cores of accumulated  $\beta$ -amyloid peptide in the perikarya and adjacent nerve processes

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 147.*



## TYPES OF GLIAL CELLS

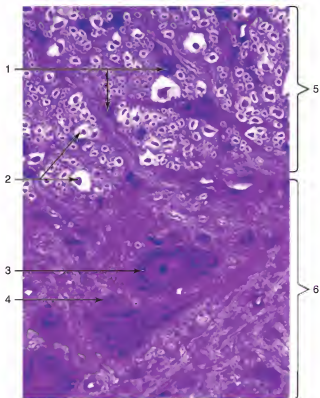
1. Astrocyte
2. Perivascular feet
3. Capillary
4. Axon
5. Oligodendrocyte
6. Myelin sheath
7. Microglial cell
8. Ependymal cells
9. Central canal or ventricle of CNS

**Key Points:** Throughout the CNS (brain and spinal cord), four types of glial cells are present:

- **Astrocytes** have supportive roles for neurons and serve to help organize the embryonic CNS. They either have many short, branching processes (**protoplasmic astrocytes**, mainly in gray matter) or fewer long processes (**fibrous astrocytes**, mainly in white matter). All astrocytic processes are reinforced by the intermediate filament protein **glial fibrillary acidic protein** (GFAP), a marker for this cell type. Termini of astrocytic processes are expanded and form a covering layer (1) over neuronal surfaces lacking myelin or synapses, (2) of **perivascular feet** around capillaries, contributing to the **blood-brain barrier**, and (3) lining the inner meningeal layer on the surface of the CNS as the **glial limiting membrane**.
- **Oligodendrocytes** extend flattened membranous processes to form **myelin sheathes** around nearby axons. Lipid-rich myelin causes the appearance of white matter.
- **Microglial cells** are monocyte-derived and provide immune defenses within the CNS.
- **Ependymal cells** form a nonepithelial lining of the fluid-filled **ventricles** of the brain and **central canal** of the spinal cord, usually with cilia to move cerebrospinal fluid. **Tanycytes** are ependymal cells of the third ventricle that also extend long processes into the neuropil.

**Clinical Note:** Microglial cells proliferate at sites of brain injury or infection by bacteria or viruses, forming **microglial nodules** around dead and dying neurons.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 147-151.*



## WHITE AND GRAY MATTER

1. Oligodendrocytes
2. Myelin sheathes
3. Neuron
4. Astrocyte
5. White matter
6. Gray matter

**Key Points:** Unstained nervous tissue in the CNS can usually be described as either “gray” or “white.” This section of spinal cord shows the cellular nature of these areas. **Gray matter** contains:

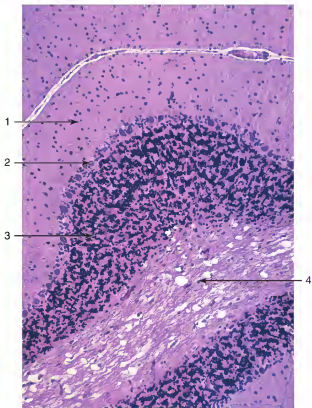
- abundant cell bodies of **neurons**, with functionally related neurons often clustered in dense aggregates called **nuclei** or organized in **layers**, as in the cerebrum;
- numerous **astrocytes**, adding to the dark appearance of the tissue; and
- large numbers of dendritic and astrocytic **processes** in neuropil.

### **White matter:**

- consists largely of **oligodendrocytes** with **myelin sheathes** that surround axons extending from cell bodies in the gray matter; and
- Is often present as large **tracts** containing parallel bundles of myelinated axons extending from aggregated perikarya. Axons in the tracts of white matter shown in the figure appear in cross-section and are surrounded by the space from which the myelin sheath has been dissolved during slide preparation.

**Clinical Note:** **Multiple sclerosis (MS)** is a chronic disease caused by progressive demyelination of axons in the white matter of the brain and spinal cord. MS involves T lymphocyte and macrophage migration to the affected sites, with the T cells inducing apoptosis in oligodendrocytes and macrophages stripping degenerating myelin from axons. Demyelination interferes with axonal impulse conduction and causes disorders in motor, ocular, and other functions.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 152-153.*





## CEREBELLUM

1. Molecular layer
2. Layer of Purkinje cells
3. Granular layer
4. Medulla with myelinated axons

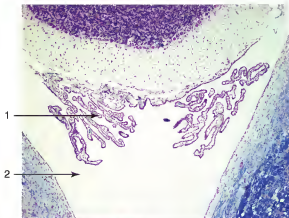
**Key Points:** The **cerebellum** modulates and coordinates the activity of skeletal muscles throughout the body. The cerebellar **cortex** is histologically distinctive, with:

- an outer **molecular layer** consisting of scattered small neurons embedded in neuropil;
- an inner **granular layer** consisting of very small, densely packed neurons; and
- between these two layers, very large and unique neurons called **Purkinje cells**, each with highly branched dendrites extending into the molecular layer and an axon entering the granular layer.

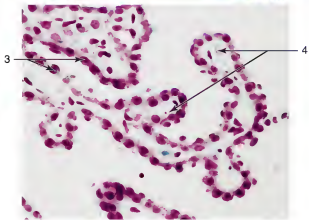
Axons from the Purkinje cells and other neurons of the cerebellar cortex are myelinated and exit in tracts located in the **medulla**.

**Clinical Note:** Chronic alcoholism can lead to **cerebellar degeneration** due to the loss of Purkinje cells in the cerebellar cortex. Loss of these cells is related to the effect of alcohol interfering with intestinal absorption of thiamine, which is needed for Purkinje cell survival and function.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 153-155.*



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## CHOROID PLEXUS

1. Villi of choroid plexus
2. Ventricle
3. Ependymal cells
4. Capillaries

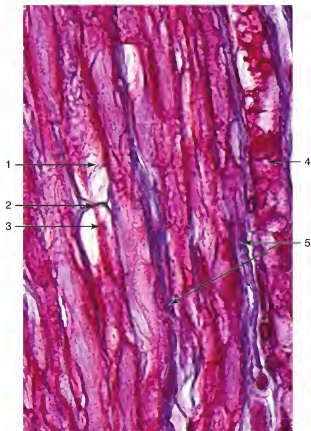
**Key Points:** The **choroid plexus** is a unique tissue projecting with elaborate folds and many **villi** into the fluid-filled **ventricles** of the brain. Villi of choroid plexus consist of the following:

- A single layer of **ependymal cells** resembling simple cuboidal epithelium but lacking a basement membrane
- A thin layer of **pia mater**, the innermost meningeal layer, in direct contact with the ependymal cells
- Loops of **capillaries** in the underlying layer of meningeal tissue

The function of the choroid plexus is the transport of water and ions from plasma in the capillaries and its release in the ventricle as the essentially cell-free **cerebrospinal fluid (CSF)**. CSF is produced continuously in the choroid plexi and circulates through the ventricles and central canal, from which it enters the subarachnoid spaces within the meninges for reabsorption into the venous circulation.

**Clinical Note:** Tumors involving the choroid plexus are most commonly benign **papillomas** occurring most frequently in children, although malignant choroid plexus **carcinomas** also occur.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 154 and 158.*



## PERIPHERAL NERVE

1. Myelin sheath
2. Node of Ranvier
3. Axon
4. Capillary
5. Endoneurium

**Key Points:** A **peripheral nerve** is part of the peripheral nervous system and has the following features:

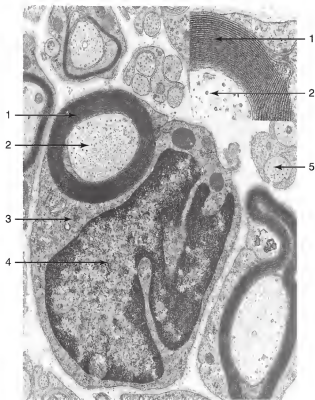
- Peripheral nerves contain axons ("fibers") of motor, sensory, or autonomic nerves. Large nerves may have all three types.
- Neuronal cell bodies of **motor nerves** are located in the spinal cord. Those of **sensory and autonomic nerves** are in the spinal ganglia and autonomic ganglia, respectively.
- Axons are always enclosed within **Schwann cells** (neurolemmocytes).
- Large-diameter axons are wrapped in multiple layers of Schwann cell membrane, which compose **the myelin sheath**.
- The small gaps between successive Schwann cells in the myelin sheath along an axon are called **nodal gaps**, or **nodes of Ranvier**. At these sites, axons have higher concentrations of  $\text{Na}^+$  channels, which allow recharging of the action potential.

Peripheral nerves also contain **connective tissue**, organized into three regions or layers:

- A sparse layer of loose connective tissue immediately around the Schwann cells is the **endoneurium**, in which capillaries are present.
- Axons, Schwann cells, and endoneurium are bundled together by a layer of **perineurium** consisting of flattened epithelial-like cells that form a diffusion barrier. Such a bundle may comprise a very small nerve itself or one **fascicle** of a larger nerve.
- A dense irregular layer called **epineurium** surrounds the perineurium. In large nerves, the epineurium encloses all of the fascicles and contains blood vessels.

**Clinical Note:** Long-standing diabetes frequently produces **peripheral neuropathy**, with axon degeneration and segmental demyelination, although the factors causing this condition are not clear. The neuropathy leads initially to decreased sensation in distal extremities.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 158-163.*



## PERIPHERAL NERVE FIBERS

1. Myelin
2. Axoplasm of myelinated fiber
3. Schwann cell cytoplasm
4. Schwann cell nucleus
5. Unmyelinated nerve fiber

**Key Points:** The axons of a peripheral nerve fall into two categories based on their size and the nature of their association with the Schwann cells:

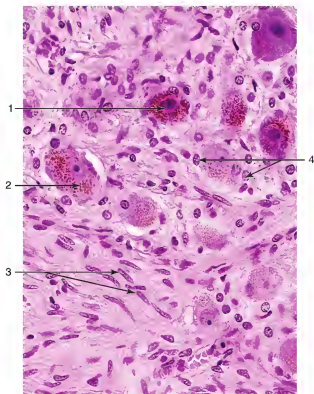
- Large-diameter axons are referred to as **myelinated fibers** because the associated Schwann cells form a multilayered myelin sheath around them. Each myelin sheath consists of a series of Schwann cells separated by nodal gaps (or nodes of Ranvier).
- Small-diameter axons can be referred to as **unmyelinated fibers** because the associated Schwann cells do not form the multiple wrappings of myelin. Instead, these cells simply engulf and surround regions of two or more small axons, without forming layers of myelin. The Schwann cells along unmyelinated fibers are not separated by distinct nodal gaps.

Transmission electron microscopy reveals that in both types of fibers, the axoplasm contains microtubules and smaller microfilaments and the Schwann cells are surrounded by an external lamina resembling the basal lamina of an epithelium.

**Clinical Note:** After injury to a peripheral nerve, **regeneration of axons** and restoration of function occurs more readily than in the CNS, partly due to guidance of the regrowing axons by the associated Schwann cells and their external laminae.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 159-160.*

(Image used with permission from Mary Bartlett Bunge, The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine.)





## PERIPHERAL GANGLION CELLS

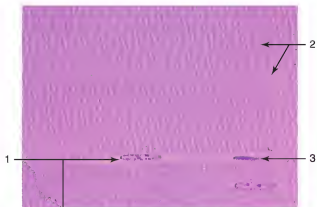
1. Neuron
2. Lipofuscin
3. Schwann cells
4. Satellite cells

**Key Points:** **Peripheral ganglia** contain the cell bodies of the sensory or autonomic neurons in the peripheral nervous system. These ganglia are covered by thin capsules of dense irregular connective tissue and contain fibroblasts and other connective tissue components with continuity to the supporting layers of the nerves that extend from the ganglia.

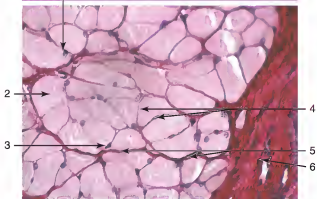
**Neuronal cell bodies** in peripheral ganglia are always very large cells. Those in dorsal root ganglia (sensory), as seen in the figure, often contain deposits of **lipofuscin**. The perikarya are surrounded by a single layer of small **satellite cells**, which like **Schwann cells** are derived from embryonic neural crest cells. Satellite cells insulate, nourish, and regulate the neuronal microenvironment in ganglia.

**Clinical Note:** Following infections of **varicella zoster virus** (chickenpox) affecting skin, the virus may undergo retrograde transport in sensory axons and become dormant for long periods in the neuronal cell bodies of the dorsal root ganglia. Viral reactivation can occur in the sensory nerves of older adults and lead to **shingles**, a condition in which the virus is redistributed to the associated nerves and skin, causing pain and itching.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 161-163.*



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## SKELETAL (STRIATED) MUSCLE

1. Nuclei of muscle fibers
2. Striated muscle fibers
3. Nucleus of fibroblast in endomysium
4. Endomysium surrounding individual muscle fibers
5. Perimysium surrounding a fascicle of muscle fibers
6. Epimysium

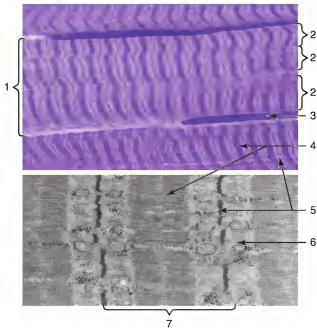
**Key Points:** Skeletal muscle consists of large cylindrical, **multinucleated fibers**. The nuclei are located peripherally, against the fiber's cell membrane or **sarcolemma**. The sarcoplasm of skeletal fibers is highly organized, with a regular pattern of alternate dark- and light-staining **striations**.

Connective tissue of skeletal muscle is located in three regions or layers:

- **Endomysium** is a delicate layer of loose connective tissue immediately surrounding the external lamina of each muscle fiber. Capillaries bringing  $O_2$  and nutrients to muscle fibers are located in the endomysium.
- **Perimysium** is a thin layer of dense irregular connective tissue that surrounds a bundle of muscle fibers comprising a **fascicle**. The perimysium includes blood vessels serving the capillary beds of the endomysium.
- **Epimysium** is a thicker layer of dense connective tissue around the entire muscle. The epimysium of many muscles is continuous with tendons at **myotendinous junctions**, which link skeletal muscle to bones.

**Clinical Note:** The organization of sarcoplasm in skeletal muscle fibers involves the cytoskeletal components. A protein called **dystrophin** helps anchor the cytoskeleton to the sarcolemma and proteins in the external lamina. Research on **Duchenne muscular dystrophy** revealed that mutations in the dystrophin gene lead to defective linkages between the cytoskeleton and the extracellular matrix. Muscle contractions can disrupt these weak linkages, which leads to the atrophy of the muscle fibers typical of this disease.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 167-168.*



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## ORGANIZATION OF SKELETAL MUSCLE FIBERS

1. Muscle fiber
2. Myofibrils
3. Nucleus of muscle fiber
4. A bands
5. Z lines
6. I band
7. Sarcomere

**Key Points:** The sarcoplasm of each skeletal **muscle fiber** is organized into parallel **myofibrils** among which the striations are generally aligned. Myofibrils are surrounded by very thin layers of sarcoplasm containing the sarcoplasmic reticulum and other organelles. Each myofibril consists of a long series of contractile units called **sarcomeres**, which can be seen by light microscopy.

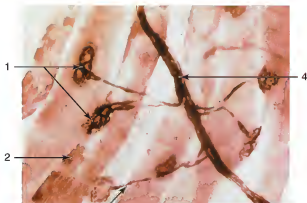
Transmission electron microscopy shows that sarcomeres are organized as follows:

- Both ends of each sarcomere have a very dense **Z line** composed of  $\alpha$ -actinin, to which actin filaments are bound.
- From both sides of the Z line, parallel **actin** filaments known as **thin myofilaments** extend across a light-staining zone, called the **I band**.
- The thin filaments extend into a dark-staining zone called the **A band**, which consists largely of **thick filaments** with parallel bundles of **myosin**. The “head” of each myosin molecule projects from the bundle and, when  $\text{Ca}^{2+}$  ions are present, binds actin in the thin filaments extending among the thick filaments.

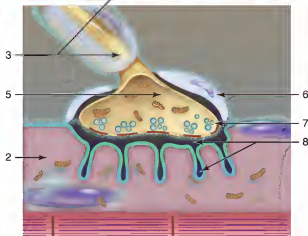
Upon neural stimulation, the muscle contracts as the thin actin filaments of each sarcomere are pulled along the thick myosin filaments. This movement causes the I bands (and the sarcomere overall) to get shorter as the muscle contracts.

**Clinical Note:** Within hours after death, when blood circulation stops and skeletal muscle fibers are deprived of  $\text{O}_2$  and nutrients,  $\text{Ca}^{2+}$  ions leak from their storage sites in the sarcoplasmic reticulum. This uncontrolled release of  $\text{Ca}^{2+}$  ions causes binding of the thin and thick filaments within sarcomeres and a “locked” contraction of the muscle known as **rigor mortis**. This stiffness is relieved within the next day as lysosomes of the muscle fibers break down, releasing enzymes that begin to degrade the myofilaments.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 168-172.*



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## NEUROMUSCULAR JUNCTIONS

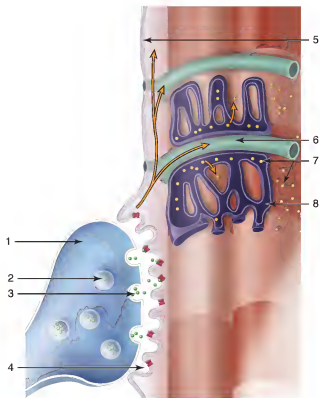
1. Neuromuscular junctions or motor end plates
2. Skeletal muscle fiber
3. Myelinated axon
4. Nerve
5. Axon terminal
6. Schwann cell
7. Synaptic vesicles
8. Synaptic cleft with junctional folds in postsynaptic membrane

**Key Points:** The ends of individual **myelinated axons** in a **nerve** that enters a fascicle of skeletal muscle fibers either form synaptic connections with individual muscle fibers or branch repeatedly and attach to many muscle fibers in a **motor unit**. The synapses between the axon terminals and the skeletal muscle fibers are called **neuromuscular junctions**, **myoneural junctions**, or **motor end plates**, each of which has the following features:

- An expanded **axon terminal**, sometimes called a bouton.
- This terminal includes many membrane-enclosed **synaptic vesicles** containing the neurotransmitter **acetylcholine**.
- A narrow space called the **synaptic cleft** between the axon terminal and the muscle fiber sarcolemma into which the neurotransmitter is secreted by exocytosis.
- The surface area of the sarcolemma postsynaptic membrane is increased via numerous **junctional folds** and has many **acetylcholine receptors**, which initiate an impulse along the sarcolemma when bound by the neurotransmitter.
- The external lamina of the **Schwann cell** around the axon terminal and that of the muscle fiber are fused, helping to prevent diffusion of neurotransmitter away from the synapse.

**Clinical Note:** A well-defined autoimmune disease called **myasthenia gravis** involves the production of antibodies against proteins of the acetylcholine receptors. Binding of these antibodies to the receptors prevents their activation by acetylcholine, leading to intermittent periods of muscle weakness. The extraocular muscles are most commonly the first affected.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 172 and 178.*



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## TRANSVERSE TUBULE SYSTEM

1. Axon terminal at neuromuscular junction
2. Synaptic vesicle
3. Neurotransmitter
4. Synaptic cleft
5. Sarcolemma of muscle fiber
6. Transverse (T) tubule
7. Calcium ions
8. Sarcoplasmic reticulum

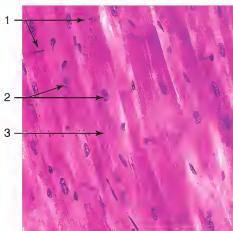
**Key Points:** The neurotransmitter acetylcholine is released by exocytosis from **synaptic vesicles** of the **axon terminal** of a motor end plate and binds receptors on the sarcolemma after diffusing across the **synaptic cleft**. The functional interaction between the synapse and the sliding filaments of the sarcomere is provided by the system of **transverse or T tubules**. T tubules are long, finger-like invaginations of the striated muscle fiber's sarcolemma that penetrate between the myofibrils. When an action potential is produced in the sarcolemma at a motor end plate, it travels to the interior of the fiber along the T tubules and causes the release of **stored  $\text{Ca}^{2+}$  ions** from terminal cisternae of the **sarcoplasmic reticulum** surrounding myofibrils.

The  $\text{Ca}^{2+}$  ions allow interaction between actin of the thin filaments and myosin of the thick filaments, and the two filaments slide past one another in an ATP-requiring process.  $\text{Ca}^{2+}$ -ATPase pumps in the terminal cisternae membranes then sequester the calcium again, and the cycle is repeated.

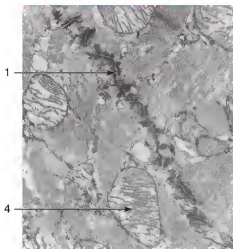
Control of  $\text{Ca}^{2+}$  ion release by the T tubule system allows the simultaneous contraction of all myofibrils upon depolarization at the synapse, including those myofibrils deep inside the muscle fiber.

**Clinical Note:** Some neuromuscular disorders involve the **myotonia**, which is characterized by abnormally slow relaxation of muscles after contraction, such as releasing the grip of a handshake. Myotonia is commonly seen in patients with hereditary "**channelopathies**," which involve mutations in genes for the various ion transport channels in the sarcolemma and T tubule system.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 169 and 176.*



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## CARDIAC MUSCLE

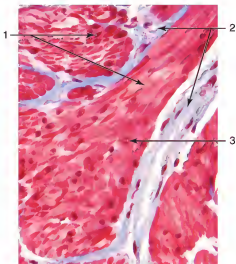
1. Intercalated disks
2. Nuclei of muscle fibers
3. Cardiac muscle fiber
4. Mitochondrion

**Key Points:** Cardiac muscle is unique to the heart myocardium and is distinguished from skeletal muscle by the following features:

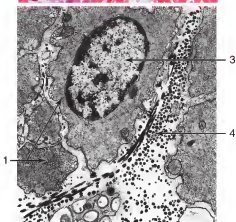
- Sarcoplasm of the fibers is divided by **intercalated disks** into regions each containing a single **nucleus** located more centrally in the fiber. Intercalated disks may be faint by light microscopy but are always more prominent than the closely repeating striations.
- Intercalated disks include the sarcolemma membranes of the two adjacent fiber regions joined firmly by **desmosomes** and by similar junctions called **fascia adherens**. Communication across the disks occurs readily via abundant areas with **gap junctions**.
- The sarcoplasm of the cardiac muscle fibers is somewhat less well organized but contains numerous **mitochondria**.
- In some regions of the myocardium, muscle fibers called Purkinje fibers are specialized for impulse conduction rather than contraction.
- **Connective tissue** organization is basically similar to that of skeletal muscle, with a well-developed vasculature.
- Unlike skeletal muscle, there is no reserve population of satellite cells between the fibers, so the regenerative capacity is severely limited.

**Clinical Note:** Because of the heart's unique role, any problem with the vascular supply of cardiac muscle that leads to **ischemia** (insufficient tissue oxygenation) is much more serious than ischemic conditions in other muscles. **Myocardial infarctions** (MI), or "heart attacks," in which disrupted blood flow in the coronary vasculature leads to localized death of the cardiac muscle, are by far the most important form of ischemic heart disease in industrialized countries.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 179-182.*



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## SMOOTH (VISCERAL) MUSCLE

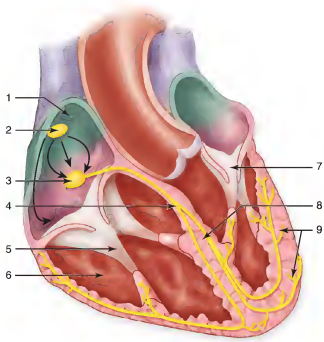
1. Smooth muscle fibers
2. Perimysium
3. Nucleus of smooth muscle fiber
4. Collagen fibers of endomysium

**Key Points:** Smooth muscle appears structurally less well organized than the other muscle types and is found primarily in the walls of the digestive, respiratory, urinary, and reproductive tracts and in the walls of blood vessels. This muscle has the following features distinguishing it from skeletal and cardiac muscle:

- The cells or fibers each have one central **nucleus** and are of much smaller diameter, with long tapering ends.
- The fibers lack striations because sarcomeres are not organized into regular units along myofibrils. Contraction involves thin actin filaments pulling along myosin filaments, but the actin filaments are bound to  $\alpha$ -actinin in **dense bodies** that are not routinely visible.
- In most smooth muscles (**single unit**), the fibers are electrically coupled via abundant **gap junctions**, which allow slow, rhythmic waves of contraction, modulated by autonomic nerves or hormones directly affecting only a few fibers.
- In certain other smooth muscles (**multiunit**), there are very few gap junctions but much autonomic innervation, so that contraction is initiated in each fiber.
- **Connective tissue** layers and organization are similar to those of other muscle types.
- The small fibers/cells can proliferate after injury, so regeneration is rapid.

**Clinical Note:** Benign tumors (noncancerous) called **leiomyomas** commonly form from smooth muscle fibers but are seldom problematic. They most frequently occur in the wall of the uterus, where they are often called **fibroids**, and here they can produce painful pressure and unexpected bleeding. Fibroids may be present in 30 to 40% of women over age 30.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 180-184.*



## HEART OVERVIEW

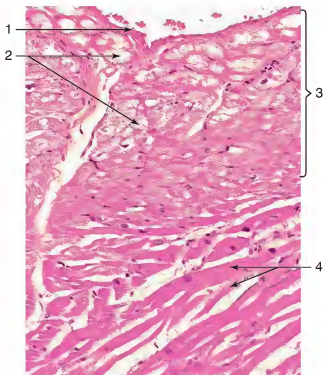
1. Right atrium
2. Sinoatrial node (pacemaker)
3. Atrioventricular node
4. Atrioventricular bundle (of His)
5. Chordae tendineae
6. Right ventricle
7. Valve
8. Interventricular septum
9. Conducting (Purkinje) fibers

**Key Points:** Histologically, the most important aspects of the heart are the following:

- The wall has three layers: an outer **epicardium**, the **myocardium**, and a lining of **endocardium**.
- The myocardium is relatively thin in the walls of the **atria**, the chambers receiving blood, and much thicker in the **ventricles**, which pump blood out of the heart.
- The endocardium is a thin layer of connective tissue lined by the **endothelium**, a simple squamous epithelium.
- The epicardium is a thicker layer of connective tissue, with much adipose tissue over the atria, and is covered by the **pericardium**, a simple squamous or low cuboidal epithelium that also lines the pericardial cavity containing the heart.
- Two specialized myocardial regions of the right atrium, the **sinoatrial** and **atrioventricular nodes**, act as **pacemaker** regions, stimulating rhythmic contractions of the entire myocardium.
- The impulses travel along specialized cardiac muscle fibers called **Purkinje fibers**, which are bundled together in the **interventricular septum** and then dispersed through the subendocardial layer of both ventricles.
- Blood leaves the atria and ventricles through **valves** which consist of endocardial leaflets of dense connective tissue that prevent backflow.

**Clinical Note:** Insufficient blood flow through the myocardial microvasculature causes tissue hypoxia (insufficient  $O_2$ ) and can produce the characteristic chest pain called **angina**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 185-187.*



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## ENDOCARDIUM AND CONDUCTING FIBERS

1. Endocardium
2. Conducting (Purkinje) fibers
3. Subendocardial conducting layer
4. Cardiac muscle fibers

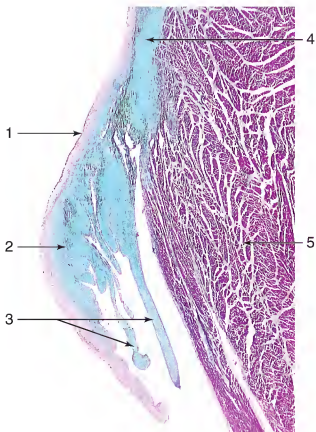
**Key Points:** The **endocardium** is a thin layer of connective tissue covered by a simple squamous **endothelium** that is continuous with the endothelium lining the major blood vessels.

Immediately beneath the endocardium of the ventricles is a network of noncontractile cardiac muscle fibers specialized for impulse conduction, the **subendocardial conducting layer**. This conducting system includes the following:

- It begins in the **sinoatrial (SA) node**, an area of cardiac muscle near the vena cava in the wall of the right atrium. This pacemaker tissue produces electrical impulses that travel through both atria along muscle sarcolemma membranes.
- At the **atrioventricular (AV) node** near the right AV valve, the impulse is sent along the specialized muscle fibers in the **bundle of His**, which extends into the **interventricular septum**.
- Left and right parts of this bundle then branch further at the heart's apex, giving rise to individual **Purkinje fibers** that extend through the **subendocardial layer** of myocardium around both ventricles.
- **Purkinje fibers** are often larger and always more pale-staining than contractile cardiac muscle fibers, containing abundant glycogen but very few myofibrils.

**Clinical Note:** **Endocarditis**, or infection of the endocardium leading to inflammation of this tissue, frequently below the valves, can occur when large numbers of bacteria enter the blood, such as after certain dental procedures. Individuals with defective heart valves characterized by a "heart murmur" are usually given prophylactic antibiotics before undergoing such dental work.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 185-188.*



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## HEART VALVE

1. Endothelium
2. Dense connective tissue of valve
3. Chordae tendineae
4. Fibrous skeleton in endocardium
5. Heart muscle (myocardium)

**Key Points:** Heart valves consist of dense connective tissue leaflets covered by **endothelium** that allow passage of blood only in one direction. The left atrioventricular (AV) valve has two such leaflets, whereas the right AV valve and both valves from the ventricles have three. The valve edges normally fit together closely when closed, preventing backflow of blood.

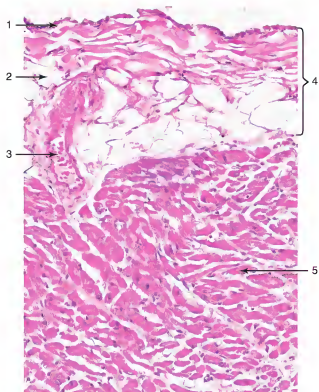
The dense connective tissue of each valve leaflet is continuous with a larger mass of dense connective tissue at the base of each valve. This **fibrous skeleton**:

- anchors each valve leaflet;
- provides a rigid framework to which myocardial tissue is attached; and
- separates and electrically insulates the myocardial tissue of the atria from that of the ventricles.

The lower surface of the leaflets making up the two AV valves each has several strands of dense connective tissue called **chordae tendineae** that attach to small projections of cardiac muscle (papillary muscles). The chordae tendineae attachments prevent the leaflets from everting and folding into the atria when the ventricles contract.

**Clinical Note:** The structure of heart valves may be slightly abnormal because of developmental defects, scarring after infections, or cardiovascular problems such as hypertension. Such **abnormal valves** may not close tightly, allowing slight regurgitation of blood back through the affected valve. This backflow of blood produces an abnormal heart sound referred to as a **heart murmur**. If the valve defect is severe, the heart will have to work harder to circulate the normal amount of blood, eventually enlarging to accommodate the increased workload. Defective heart valves often may be repaired surgically or replaced by an artificial valve or one from a large animal donor.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 187-189.*



11

## EPICARDIUM

1. Mesothelium covering epicardium
2. Adipocytes in connective tissue
3. Branch of coronary artery
4. Epicardium
5. Myocardium

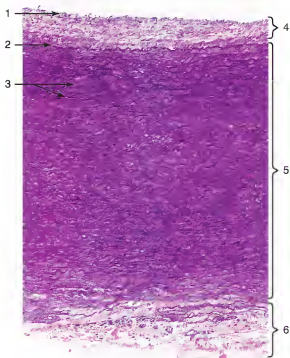
**Key Points:** The outer layer of the heart, the **epicardium**, covers the myocardium and has the following features:

- A thin layer of loose connective tissue with many **adipocytes**, especially over the atria, continuous with the connective tissue of the **myocardium**
- Location of the **coronary arteries** and smaller vessels entering the myocardium
- An outer covering of simple squamous or low cuboidal epithelium or **mesothelium**

The epithelial cells of the covering mesothelium are serous cells secreting a lubricating fluid that allows movement of the heart in the **pericardial cavity** with essentially no friction. The epicardium constitutes the visceral layer of the pericardium and is continuous with the parietal layer of pericardium that lines the pericardial cavity.

**Clinical Note:** Bacterial or viral infection of the pericardium leads to local inflammation or **pericarditis**. The inflammation may involve leakage of fluid from capillaries, producing fluid accumulation in the pericardial cavity, a condition called **cardiac tamponade**. Severe accumulation of fluid around the heart may interfere with its ability to pump blood. However, excess fluid can be removed from the pericardial cavity by aspiration. Early-stage pericarditis usually includes fever and localized chest pain and can be diagnosed with a stethoscope by characteristic rubbing sounds of pericardial friction.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 185-189.*



## WALL OF AORTA

1. Endothelium
2. Internal elastic lamina
3. Elastic sheets and fibers
4. Tunica intima
5. Tunica media
6. Tunica adventitia

**Key Points:** All blood vessels, except those of the microvasculature, have walls organized with three layers, or tunics:

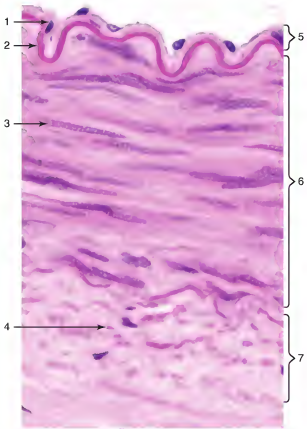
- The innermost **tunica intima** is lined by a simple squamous epithelium, or the **endothelium**, and a thin subendothelial layer of loose connective tissue.
- The middle **tunica media** is composed of helically arranged smooth muscle fibers interposed with connective tissue containing elastic lamellae or fibers.
- The external **tunica adventitia** is connective tissue that merges gradually with the surrounding stroma of the organ where the vessel is located.

The largest arteries, the **aorta**, **pulmonary artery**, and their major branches, are called **elastic arteries** and have the following characteristics:

- The subendothelial part of the tunica intima is relatively thick and is delimited from the tunica media by the **internal elastic lamina**, a fenestrated sheet of elastin.
- In the tunica media, **elastic fibers** and **lamellae** alternate with layers of smooth muscle and associated connective tissue.
- Stretching or expansion of the wall's elastic components when contraction of the ventricles (systole) fills the elastic arteries allows the wall to recoil passively during diastole, which propels blood forward and helps maintain diastolic pressure.
- Cells in large vessels' tunica adventitia and outer tunica media do not receive adequate  $O_2$  from blood in the lumen, so these layers also contain very small blood vessels, the **vasa vasorum** or "vessels of the vessels."

**Clinical Note:** Progressive age-related weakening of elastin in the abdominal aortic wall can lead to localized abnormal dilations, or **aortic aneurysms**. These can occur in various forms and are life threatening when severe and include the possibility of rupture.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 189-192.*





## WALL OF MUSCULAR ARTERY

1. Endothelium
2. Internal elastic lamina
3. Nucleus of a smooth muscle fiber
4. Connective tissue
5. Tunica intima
6. Tunica media
7. Tunica adventitia

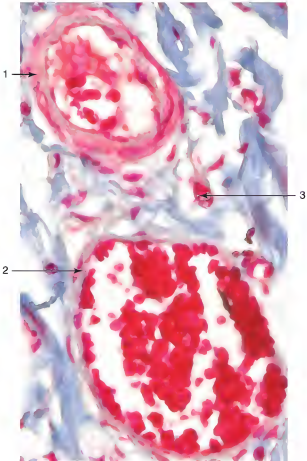
**Key Points:** Vessels branching from elastic arteries are termed **muscular arteries**. Although an **internal elastic lamina** and other elastic components are still present, the three major **tunics** are thinner than in elastic arteries. **Smooth muscle** predominates in the **tunica media**, where from 4 to 40 circular or spirally arranged muscle layers may be present, interspersed with small amounts of **connective tissue**, which also forms a tunica adventitia.

Blood pressure and local blood flow in organs are regulated by changes in the lumen of muscular arteries, produced by local contraction (for **vasoconstriction**) or relaxation (for **vasodilatation**) of the arteries' smooth muscle. The muscle activity is controlled by autonomic innervation in the tunica adventitia and local cell interactions. In muscular arteries, small changes in the size of the lumen greatly affect the blood flow and the distribution of  $O_2$  and nutrients to tissues downstream.

**Clinical Note:** **Atherosclerosis**, which is involved in over 50% of all deaths in the United States, is a disease primarily affecting elastic arteries, such as the aorta and carotid arteries, and the large to medium-sized muscular arteries, such as the coronary arteries. The basic problem is a **fibrous-fatty plaque**, or **atheroma**, which forms slowly within the tunica intima and, although variable, consists of fibrous connective tissue and smooth muscle covering a necrotic region of lipid (mainly cholesterol), cell debris, and macrophages (or foam cells) filled with lipid droplets.

Plaques in the smaller muscular arteries can eventually occlude blood flow to distal tissues, as with coronary arteries and **ischemic heart disease**. In larger arteries, atheromas produce localized destruction of the wall, weakening it and causing **aneurysms**. Portions of atherosclerotic plaques can also detach and cause obstruction, called an **embolism**, of smaller vessels downstream.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 192-193.*



11

## ARTERIOLE AND VENULE

1. Arteriole
2. Venule
3. Capillary

**Key Points:** Arterioles are the smallest branches of a muscular artery and are the components of an organ's **microvasculature** that bring blood to the **capillaries** for exchange of  $O_2$ ,  $CO_2$ , nutrients, and wastes between blood and tissue fluid. Arterioles have:

- only one to three layers of closely packed smooth muscle fibers in the tunica media, with very little elastin;
- a size generally less than 0.5 mm in diameter;
- lumens *approximately* as wide as the wall is thick; and
- very thin tunica intima and inconspicuous tunica adventitia.

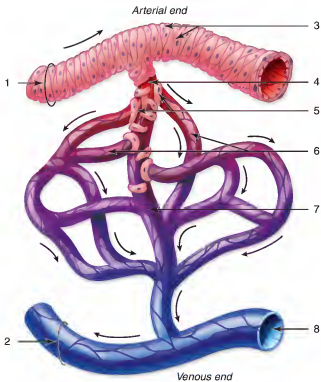
**Venules** drain blood from an organ's microvasculature, beginning the blood's return to the heart. **Postcapillary venules** drain capillaries directly and:

- range from 15 to 20  $\mu m$  in diameter;
- have scattered contractile **pericytes** surrounding the endothelium;
- have very thin walls and large lumens in comparison with arterioles; and
- are the primary sites at which white blood cells exit the vasculature at sites of infection or tissue damage.

Postcapillary venules converge into **collecting venules**, with more contractile cells, and these converge further to form **muscular venules**, which have a tunica media with two or three layers of smooth muscle cells. The large luminal diameter and thin wall are characteristic of all venules.

**Clinical Note:** Blood pressure depends on cardiac output and the **total peripheral resistance** to blood flow. The latter variable depends mostly on the resistance of arterioles, which is determined largely by their lumen size. Blood pressure is normally controlled primarily by factors regulating arteriolar vasoconstriction and vasodilation. **Hypertension**, or the chronic elevation of blood pressure, may be secondary to renal or endocrine disorders but is much more commonly **essential hypertension**, due to a wide variety of mechanisms that produce vasoconstriction.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 193-199.*



## COMPONENTS OF MICROVASCULATURE

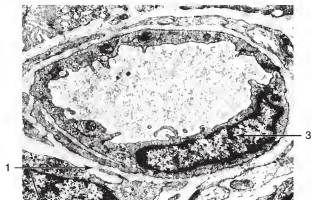
1. Arteriole
2. Postcapillary venule
3. Smooth muscle fibers
4. Metarteriole
5. Precapillary sphincters
6. Capillaries
7. Thoroughfare channel
8. Endothelial cells

**Key Points:** Every organ contains a microvasculature that allows exchange of  $O_2$ ,  $CO_2$ , and metabolites between blood and cells in the local microenvironments. Vessels of the microvasculature are all lined by **endothelium**, but other characteristics depend on their position in the blood delivery system:

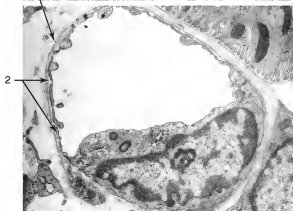
- **Arterioles** typically have one to three layers of **smooth muscle fibers**.
- Smaller branches of arterioles, sometimes termed **metarterioles**, have less muscle overall and branch further as **capillaries**. Smooth muscle fibers at the branch points form **precapillary sphincters** that contract rhythmically and provide pulsatile blood flow into the network of capillaries.
- The metarteriole may lead to a central channel lacking precapillary sphincters called a **thoroughfare channel**.
- Capillaries consist of a layer of very thin endothelial cells, with a basal lamina that also encloses scattered mesenchymal cells called **pericytes** used to produce new smooth muscle during microvascular remodeling.
- Each capillary network converges with the distal thoroughfare channel, which drains into a **postcapillary venule**. These are typically 15 to 20  $\mu m$  in diameter, with pericytes but no smooth muscle.

**Clinical Note:** The structural components of an organ's microvasculature can be quickly modified in response to developmental or pathologic changes in the organ. **Angiogenesis**, the growth of new capillaries from preexisting capillaries or arterioles is necessary for continuous **tumor growth** and is a research target in new treatments for various cancers.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 193-199.*



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## CONTINUOUS AND FENESTRATED CAPILLARIES

1. Basal lamina surrounding capillary
2. Fenestrations
3. Nucleus of endothelial cell

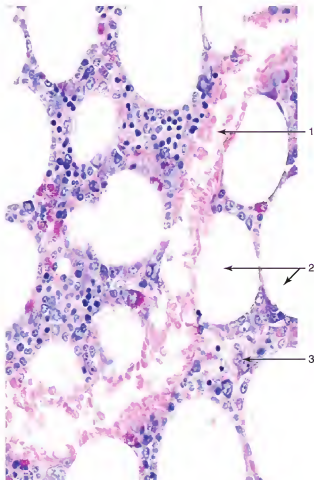
**Key Points:** The microvasculature of most organs contains capillaries approximately 5 to 10  $\mu\text{m}$  in diameter that may be either of two types: continuous or fenestrated.

- Most tissues are supplied by **continuous capillaries**, in which all of the **endothelial cells** are tightly joined (by **zonulae occludens**), and allow free exchange of  $\text{O}_2$  and  $\text{CO}_2$ , but movement of other material across the endothelium is regulated via mechanisms such as pinocytosis.
- Organs whose function requires rapid and extensive molecular exchange with the blood, such as the kidneys and all endocrine glands, have **fenestrated capillaries**, in which the **endothelial cells** are very thin and have variable numbers of perforations called **fenestrations**. The fenestrations in capillaries from different organs range from 30 to 80  $\mu\text{m}$  in diameter and may include very thin, nonmembranous diaphragms.

Both types of capillaries are completely surrounded by a continuous basal lamina produced by the endothelial cells.

**Clinical Note:** A consistent feature of **diabetes** is a diffuse thickening of the capillary basal laminae and concomitant decrease in metabolic function, particularly in capillaries of the retina, kidney, striated muscle, and skin. This characteristic **diabetic microangiopathy** is related to **hyperglycemia**, or excessive blood glucose, which is part of diabetes. Among the effects of chronic hyperglycemia is the more rapid formation of sugar-derived **advanced glycation end-products**, some of which can react with and cross-link basal lamina components and interfere with endothelial cell metabolism and function.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 194-198.*



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## SINUSOID

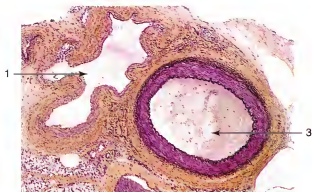
1. Sinusoid
2. Adipocytes
3. Bone marrow

**Key Points:** In organs where the function involves maximal exchange of macromolecules, as in the liver, or extensive cell movement from the stroma into blood, as in the **bone marrow**, the microvasculature includes discontinuous capillaries or **sinusoids**. Two points of interest regarding sinusoids are as follows:

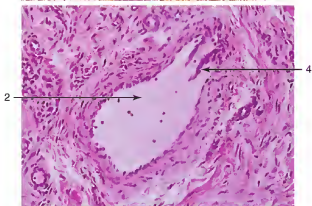
- They not only have fenestrated endothelial cells, but they also have large (30–40  $\mu\text{m}$ ) irregular spaces between these cells.
- The basal lamina of their endothelium may be thin and discontinuous or absent altogether.

**Clinical Note:** Hepatic sinusoidal obstruction syndrome is a disorder that occurs in the sinusoids of liver lobules. In recent years, the condition is seen most commonly in patients who have undergone chemotherapy or radiotherapy and bone marrow transplantation. The disease seems to result from toxic damage to the sinusoidal endothelial cells, which allows leakage of erythrocytes into the perisinusoidal space. This leads to activation of the coagulation cascade, local accumulation of debris and macrophages, and obstruction of the sinusoids, which interferes with hepatic function.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 195–197.*



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## VEINS

1. Medium vein
2. Small vein
3. Muscular artery
4. Valve

**Key Points:** Veins are most often classified by their size:

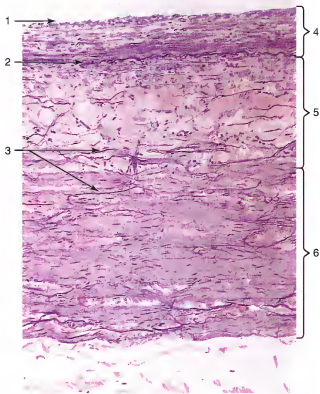
- The venules draining an organ's microvasculature join to form **small veins** with a sparse layer of smooth muscle cells around the endothelium.
- Small veins converge further to form **medium veins** with a thicker, more prominent layer of smooth muscle in the tunica media. Most named veins are medium veins, with diameters of up to 10 mm that leave the organs and enter the venous system carrying blood back to the heart.
- Veins with diameters larger than 10 mm, such as the vena cava, are the **large veins**, in which the tunica media is relatively thin and the thickest layer of the wall is the tunica adventitia.

Other features to note regarding veins include:

- Thin folds of the tunica intima extend into the lumen bilaterally as **valves**, which prevent backflow of blood. Valves are more abundant in the lower part of the body where blood returning to the heart moves a greater distance against gravity.
- Medium and large veins usually closely accompany an organ's corresponding arteries.
- Compared to the corresponding muscular arteries, the **tunica media is much thinner** in medium veins.
- **Lumens are larger** in venules and veins than in the corresponding arterioles and muscular arteries.

**Clinical Note:** Chronically elevated intraluminal pressure can produce **varicose veins**, a condition in which the veins are abnormally dilated and valves are subsequently less functional. Occurring most commonly on the superficial veins of the legs, sluggish blood flow in varicose veins can lead to **thrombosis** or clotting on the vessel wall, although clot detachment to form an **embolism** is rare.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 198-200.*



11

## WALL OF VENA CAVA

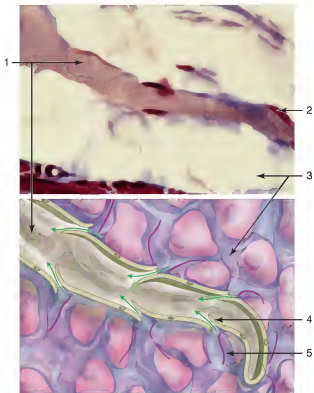
1. Endothelium
2. Internal elastic lamina
3. Elastic fibers
4. Tunica intima
5. Tunica media
6. Tunica adventitia

**Key Points:** The walls of **large veins**, such as the vena cavae and subclavian veins, typically have the following features:

- The **tunica media** is somewhat thin compared to the **tunicae intima and adventitia**.
- An **internal elastic lamina** is present surrounding the tunica intima but less distinct than in arteries as a boundary between the tunics.
- The tunica media contains alternating layers of **smooth muscle** and **elastic fibers**, although these are not as well organized as in arteries.
- The **tunica adventitia** is the thickest layer and contains longitudinally arranged smooth muscle and elastic fibers, along with the dense irregular connective tissue.

**Clinical Note:** Inflammation, thrombosis, and aneurysms are relatively rare occurrences in the large veins. Medical issues directly involving the vena cavae usually stem from **congenital anomalies** due to defects in one of the several developmental transformations that normally occur during embryonic formation of these large vessels. Medical problems may also arise from decreased blood flow after **compression of the vena cavae** by abnormalities in surrounding organs, such as tumors, aortic aneurysms, or a gravid uterus.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 191, 198, and 200.*



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## LYMPHATIC CAPILLARY

1. Lymphatic capillaries
2. Nucleus of endothelial cell
3. Connective tissue with interstitial fluid
4. Valve between endothelial cells
5. Anchoring filament

**Key Points:** Excess interstitial fluid that forms in tissues is returned to the blood circulatory system as **lymph** carried by **lymphatic vessels**. Lymph is initially collected from the interstitial space of connective tissue by **lymphatic capillaries**. These are numerous and have:

- walls consisting only of a very thin **endothelium** with an incomplete basal lamina;
- lumens held open by elastic **anchoring filaments** from the basal lamina to surrounding connective tissue; and
- openings between the endothelial cells partially covered by cellular folds acting as **valves**, through which fluid enters the vessel.

Lymphatic capillaries converge as increasingly larger lymphatic vessels, with **lymph nodes** located at major points of convergence. As the lymphatics become larger, their walls begin to resemble those of veins:

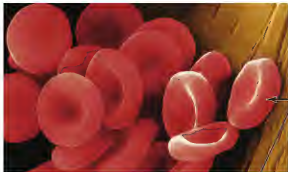
- Larger lymphatic vessels have thin walls, with the three poorly defined tunics.
- The tunica intima is folded to form valves that prevent backflow of lymph.
- The lumens of lymphatic vessels are usually large.
- As with veins, lymphatic flow is aided by external forces, such as surrounding muscle contractions or movements of other organs.

The largest lymphatic vessels, the thoracic and right lymphatic ducts, empty into the junction of the left subclavian and jugular veins, returning lymph to blood.

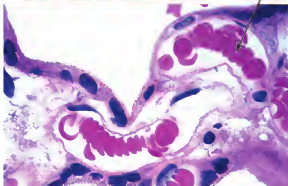
**Clinical Note:** Lymphatic capillaries are clinically important because they facilitate the spread of microorganisms, parasites, or malignant cells in the body. Surgical removal of lymph nodes, for example, to check for metastasis of cells from a nearby tumor, can disrupt the lymphatic drainage and produce swelling, or **lymph edema**, in tissues of the affected region.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 198-202.*

1. What protein fills the cytoplasm of these cells and provides their normal red color?
2. Lacking organelles, these cells are functional for approximately how long?



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## ERYTHROCYTES

1. Hemoglobin
2. 120 days
3. Erythrocytes

**Key Points:** By far the most abundant blood cell, **erythrocytes** (or **red blood cells**) are:

- flexible, **biconcave disks**, approximately  $7.5\ \mu\text{m}$  in diameter;
- terminally differentiated, having lost their nuclei during their development; and
- lacking organelles but packed with the tetrameric,  $\text{O}_2$ -carrying protein **hemoglobin**.

The normal concentration of erythrocytes in blood is **4 to 6 million/ $\mu\text{L}$** . Transmembrane proteins such as glycophorin A and an ion channel called band 3 protein have extracellular antigenic sites that differ among individuals and form the basis for the **ABO blood typing system**. A protein of the inner cell membrane, **spectrin**, was first discovered in erythrocytes but is also present in many cells where it is important in organizing and maintaining both the cytoskeleton and the cell membrane.

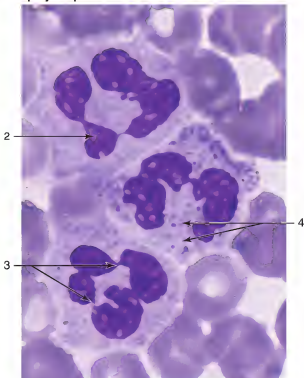
Because these organizing factors and ion channels cannot be replaced in erythrocytes by newly made proteins, their loss after approximately 4 months leads to disorganization of the membrane, swelling of the cells, and removal by macrophages.

**Clinical Note:** **Anemia** is a medical disorder caused by abnormally low capacity for  $\text{O}_2$  transport in blood, usually due to a decreased number of erythrocytes. A common cause of anemia is a deficiency of **iron**, a necessary cofactor for functional hemoglobin.

**Sickle cell disease** is caused by a point mutation in erythrocyte stem cells that yields a single amino acid substitution in hemoglobin. In individuals homozygous for this trait, deoxygenation of the red blood cells in the microvasculature leads to abnormal polymerization of the altered hemoglobin, producing rigid aggregates that make the cells less flexible and greatly change the cell shape. Such cells can block capillaries, restricting  $\text{O}_2$  delivery to tissues and leading to varying degrees of ischemia and organ damage.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 204-206.*

1. What are these cells with characteristic "polymorphic nuclei"?



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## NEUTROPHILS

1. Neutrophils
2. Multilobed nucleus
3. Strands of chromatin and nuclear envelop between nuclear lobes
4. Cytoplasmic granules

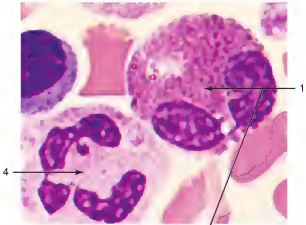
**Key Points:** Neutrophils are the most numerous **granulocytes**, which are the **leukocytes** (**white blood cells**) with abundant, granule-filled cytoplasm. Neutrophils:

- typically make up 60 to 70% of the circulating leukocytes;
- have characteristic **polymorphic nuclei** with two to five lobes connected by extensions of chromatin and nuclear membrane;
- variable diameters (9-15  $\mu\text{m}$ ) on blood smears; and
- cytoplasm filled with poorly stained granules of two types:
  - **azurophilic granules**, which are specialized lysosomes for killing ingested bacteria; and
  - smaller **specific granules** containing components for exocytosis at sites of infection for antibacterial activity and other mechanisms of immune defense.

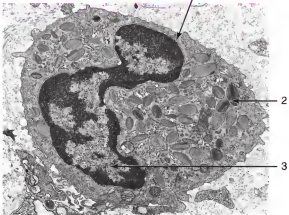
Neutrophils typically circulate for several hours in the blood and then become functional only after leaving the circulation by **diapedesis** or transmigration between the endothelial cells of venules at sites of infection or tissue damage. There these cells accumulate and actively pursue and **phagocytose bacterial cells**. Depending on their level of phagocytic activity, neutrophils function in tissues for only 1 to 4 days before undergoing **apoptosis**. Masses of active and dying neutrophils may accumulate at sites of infection to form **pus**.

**Clinical Note:** Several kinds of **neutrophil defects**, often genetic in origin, can affect function of these cells, for example, by decreasing adhesion to the wall of venules, by causing the absence of specific granules, or by causing deficits in certain factors of the azurophilic granules. Individuals with such disorders typically have more frequent and more persistent bacterial infections, although macrophages and other leukocytes may substitute for certain neutrophil functions.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 206-210.*



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## EOSINOPHILS

1. Eosinophils
2. Eosinophilic granules
3. Bilobed nucleus
4. Neutrophil

### Key Points: Eosinophils:

- typically make up only 2 to 4% of circulating leukocytes;
- have characteristic **nuclei with two large, interconnected lobes**;
- are similar in size to neutrophils or are slightly larger; and
- have cytoplasm filled with very **eosinophilic-specific granules**.

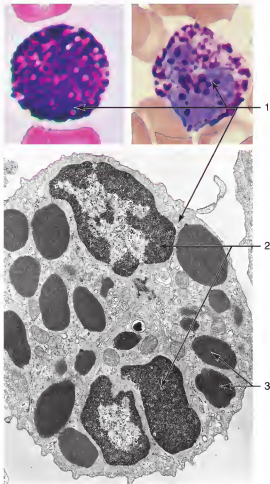
Like neutrophils and other leukocytes, circulating eosinophils leave the blood and function at sites of infection and inflammation. The acidophilic nature of these cells' granules is due to their abundant content of **major basic protein**, also known as proteoglycan 2. Ultrastructurally, the specific granules of eosinophils show a characteristic oval shape, with a disk-shaped electron-dense core.

Major dense protein and various enzymes in these granules undergo exocytosis at sites of infection and help mediate the following functions of eosinophils:

- They have **toxic effects against helminthic worms** and certain other parasites.
- They help modulate the phagocytic activity of neutrophils and macrophages.
- They trigger histamine release from basophils and mast cells.

**Clinical Note:** Eosinophilia, an increase in the absolute number of these cells in the circulation, can indicate a parasitic infestation, particularly in tropical regions where conditions for such infections are most common. Eosinophils play a major role in controlling the growth of various parasites such as schistosome worms, which cause chronic **schistosomiasis**. Other causes of eosinophilia include specific allergies and certain malignancies.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 208-210.*



## BASOPHILS

1. Basophils
2. Bilobed nucleus
3. Basophilic granules

**Key Points:** The third type of granulocyte, the **basophil**, is also the least abundant leukocyte, representing less than 1% of the total white cell count. Basophils are recognized by:

- large, **bilobed nuclei**, somewhat similar to those of eosinophils; and
- large, irregularly shaped, **strongly basophilic granules** that partially hide the nucleus.

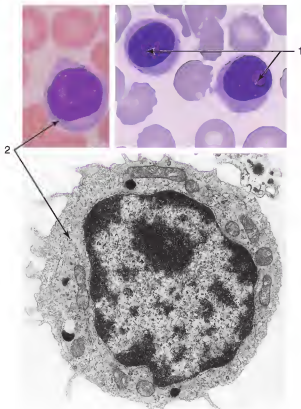
Functionally, basophils are important after leaving the circulation at sites of inflammation. The granules undergo exocytosis and release many factors involved in the **inflammatory response**, including:

- **histamine**, which immediately increases microvascular permeability;
- **heparin**, which acts to inhibit blood coagulation in the immediate area;
- **chemotactic factors**, producing accumulation of the other granulocytes;
- **platelet-activating factors**; and
- enzymes such as **acid hydrolases** and **proteases** with local inflammatory functions.

Basophils resemble and share many functions with **mast cells**, which are normal residents of the connective tissue in most organs, particularly near blood vessels. Degranulation in both cell types is triggered by cross-linking of immunoglobulin E (IgE) molecules bound to cell-surface receptors.

**Clinical Note:** Basophils and mast cells are central to **type 1 hypersensitivity**. In some individuals, substances such as certain pollen proteins or specific proteins in food are allergenic (ie, elicit production of specific IgE antibodies, which then bind to receptors on mast cells and immigrating basophils). On subsequent exposure, the allergen binds these IgE molecules, causing them to cross-link and aggregate on the cell surfaces and triggering rapid exocytosis of the cytoplasmic granules. Release of the inflammatory mediators in this manner can result in **bronchial asthma**, cutaneous **hives**, **rhinitis**, **conjunctivitis**, or allergic gastroenteritis.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 209-210.*



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3. What is the primary function of these cells?



## LYMPHOCYTES

1. Small lymphocytes
2. Medium lymphocytes
3. Produce cellular or humoral immunity

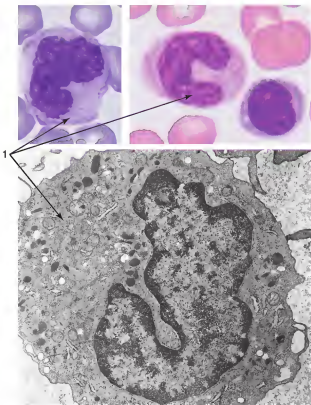
**Key Points:** Lymphocytes have almost no cytoplasmic granules and are classified as **agranulocytes**. They are abundant, representing over 25% of circulating leukocytes, and vary widely in diameter, ranging from 6 to approximately 18  $\mu\text{m}$ . Lymphocytes can be recognized by their large, **generally spherical or slightly indented nuclei**, surrounded by a relatively **small amount of cytoplasm** compared with other leukocytes.

Immunocytochemistry using antibodies against cell surface proteins demonstrates three major types of lymphocytes:

- **T lymphocytes** (T cells), which mediate **cell-mediated immunity** and include many subsets, including cytotoxic T cells and regulatory T cells.
- **B lymphocytes**, which synthesis and release specific antibodies used in **humoral immunity**. B cells sensitized against specific antigens enter connective tissue and differentiate as **plasma cells** to begin antibody production.
- **Natural killer (NK) cells**, which are less abundant lymphocytes with direct cytotoxic effects on virus-infected cells and some neoplastic cells.

**Clinical Note:** Given their central roles in immunity, lymphocytes are obviously important in many diseases. **Lymphomas** are a group of disorders involving neoplastic proliferation of lymphocytes. All lymphomas are considered malignant because they can very easily become widely spread throughout the body.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 211-212.*



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2. These circulating cells are precursors to what functional cell?

## MONOCYTES

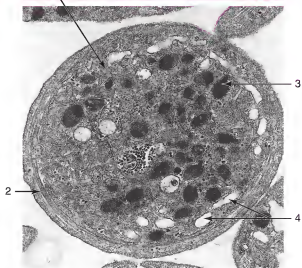
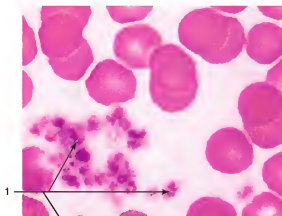
1. Monocytes
2. Macrophages

**Key Points:** Monocytes are agranulocytes that are typically much larger than most lymphocytes and less abundant, representing about 5% of circulating leukocytes. The distinguishing feature of a monocyte is the **large nucleus**, which is more **deeply indented** than that of a lymphocyte and frequently shows a distinct “C” shape. Monocytes have very few specific granules but do contain lysosomes, along with mitochondria, rough endoplasmic reticulum, and other organelles.

Monocytes leave the circulation across venule walls at sites of tissue damage or infection and become activated there as **macrophages**, which phagocytose tissue debris, apoptotic cells, bacteria, and other extraneous material and serve as important antigen-presenting cells for T lymphocytes. Monocytes also give rise to certain long-lived cells of many organs, such as microglia in the CNS, Kupffer cells of the liver, or osteoclasts. Functions of these monocyte-derived cells usually include innate immune defense and various roles in tissue repair.

**Clinical Note:** Extravasation or the accumulation of immigrating monocytes occurs in the early phase of inflammation after injury to a tissue. **Acute inflammation** is usually short-lived as macrophages undergo apoptosis or leave the site, but **chronic inflammation** usually involves the continued recruitment of monocytes. The resulting continuous presence of macrophages can lead to excessive tissue damage, which is typical of chronic inflammation.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 212-213.*



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## PLATELETS (THROMBOCYTES)

1. Platelets
2. Marginal bundle
3. Alpha granules
4. Membrane vesicles and channels

**Key Points:** Platelets (or **thrombocytes**) are nonnucleated, membrane-enclosed fragments of cytoplasm derived by the pinching off of the tips of proplatelet processes extending from megakaryocytes in bone marrow. They are **disk-like, very small** (typically 2-4  $\mu\text{m}$  in diameter), and often clumped on blood smears.

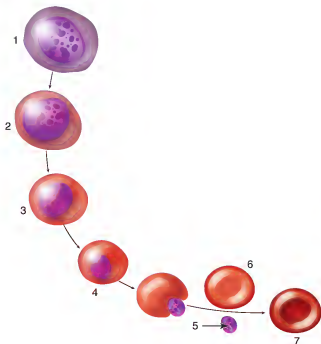
Ultrastructurally, each platelet can be seen to contain:

- a **marginal bundle** of microfilaments and microtubules, which maintain the platelet's shape and contract when platelets adhere to collagen outside of the blood vessels;
- an **open canalicular system** of membrane channels, also located peripherally and continuous with surface invaginations; and
- a more heavily stained, central **granulomere** region with various granules, of which the larger, most numerous  **$\alpha$  granules** contain platelet-derived growth factor.

The major function of platelets is to promote blood coagulation, which is particularly important in the microvasculature where minor disruptions with blood leakage are common. At such sites of vascular breaks, when platelets come into contact with collagen around the endothelium, they aggregate, contract, and immediately begin to undergo rapid disruption and granular exocytosis into the canalicular system and the microenvironment. Factors and enzymes released from the platelet granules rapidly change plasma fibrinogen to a three-dimensional meshwork of fibrin polymers that forms the basis of a **blood clot** (or **thrombus**).

**Clinical Note:** Aspirin and other nonsteroidal anti-inflammatory agents have an inhibitory effect on platelet function and blood coagulation because they block the local prostaglandin synthesis that is needed for platelet aggregation, contraction, and exocytosis at sites of injury. **Bleeding disorders** result from abnormally slow blood clotting. One such disease directly related to a defect in the platelets is a rare autosomal recessive **glycoprotein Ib deficiency**, involving a factor on the platelet surface needed to bind subendothelial collagen and begin the cascade of events leading to clot formation.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 212-215.*



## ERYTHROPOIESIS

1. Proerythroblast
2. Basophilic erythroblast
3. Polychromatophilic erythroblast
4. Orthochromatophilic erythroblast
5. Nucleus
6. Reticulocyte
7. Erythrocyte

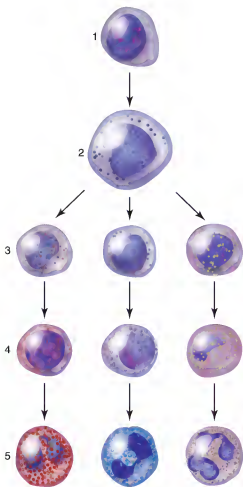
**Key Points:** Erythropoiesis occurs in **hemopoietic islands** or cords of stem and progenitor cells in the stroma of **red bone marrow**. Both cell proliferation and differentiation in this process are accelerated by the growth factor **erythropoietin** produced by cells of the kidney. The sequence of cell division and differentiation in erythropoiesis includes the following recognizable cells, which are seen on smear preparations of marrow:

- The earliest progenitor cells are the **proerythroblasts**, which are large, relatively rare, and have large nuclei and slightly basophilic cytoplasm.
- Proerythroblasts divide and produce **basophilic erythroblasts**, in which the cytoplasm is more intensely basophilic due to polyribosomes for hemoglobin synthesis.
- At the next stage, **polychromatophilic erythroblasts** have regions of both basophilic and acidophilic cytoplasm due to the accumulating hemoglobin in some areas.
- When hemoglobin uniformly fills the cytoplasm and most ribosomes are disappearing, the cells are called **orthochromatophilic erythroblasts**, a stage no longer capable of dividing.
- Late in this stage, the cell ejects its **nucleus** (which is then removed by a macrophage) and becomes a disk-shaped **reticulocyte**, which may still contain some ribosomes.

Each reticulocyte enters the circulation by crossing the endothelium of the marrow's sinusoids and quickly matures into a biconcave **erythrocyte**.

**Clinical Note:** **Anemia**, or abnormally low levels of circulating erythrocytes, is often due to a deficiency of a substrate needed for erythropoiesis. In **iron deficiency anemia**, perhaps the most common nutritional disorder, a lack of readily available iron slows differentiation, and in the **megaloblastic anemias**, division of progenitor cells is slowed by deficiencies of folic acid or vitamin B<sub>12</sub>, both of which are required for DNA synthesis.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 216-221.*





## GRANULOPOIESIS

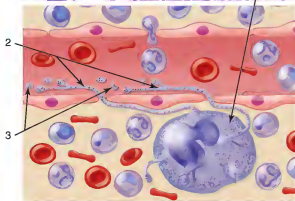
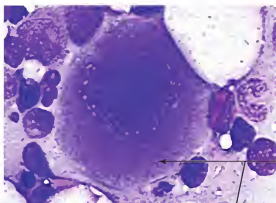
1. Myeloblast
2. Promyelocyte
3. Myelocytes (eosinophilic, basophilic, and neutrophilic)
4. Metamyelocytes (eosinophilic, basophilic, and neutrophilic)
5. Eosinophil, basophil, and neutrophil

**Key Points:** **Granulopoiesis**, or the formation of the three kinds of granulocytes, also occurs in the red bone marrow, and specific cell stages and cell types are seen in marrow smears:

- Undifferentiated and slowly dividing **myeloblasts**, with large nuclei and relatively little cytoplasm, are produced by slowly dividing progenitor cells.
- Myeloblasts give rise to **promyelocytes**, larger cells with more abundant basophilic cytoplasm containing azurophilic granules (lysosomes).
- Different sets of genes are now activated, yielding the granules characteristic of neutrophilic, eosinophilic, or basophilic differentiation in cells now called **myelocytes**.
- The myelocytes become **metamyelocytes** (with the three types recognizable by their granules) as their nuclei become constricted into either the bilobed or the polymorphic form. Immature metamyelocytic neutrophils may be released during chronic infections and are seen as circulating cells called **stab (band) cells**.
- After completing differentiation, the cells are released to the blood as mature neutrophils, eosinophils, and basophils.

**Clinical Note:** The rapid cell proliferation in granulopoiesis is adversely affected by many chemotherapeutic drugs used to treat various cancers. The white cell count can become abnormally low (**leukopenia**), with **neutropenia** leaving patient prone to various common sources of infection.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 220-223.*



## MEGAKARYOCYTES AND PLATELET FORMATION

1. Megakaryocytes
2. Proplatelets
3. Platelets

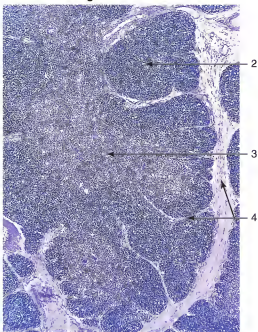
**Key Points:** Megakaryocytes are very large (50-100  $\mu\text{m}$  in diameter), relatively scarce cells of the red bone marrow stroma. Megakaryocytes are distinguished by having very large, irregular lobulated nuclei, which are polyploid. The cytoplasm is basophilic, with much rough endoplasmic reticulum. Megakaryocytes develop locally from megakaryoblasts and promegakaryocytes in a process promoted by thrombopoietin.

The function of megakaryocytes is the formation of platelets (**thrombopoiesis**). From the surface of megakaryocytes extend many long, branching processes called **proplatelets**, which can penetrate the sinusoidal endothelium to lie within the circulating blood. Cytoskeletal elements form a loop at the distal tip of the proplatelets and pinch off to release a **platelet** with its characteristic structural features. Proplatelet elongation and the serial release of many platelets occur very rapidly during thrombopoiesis.

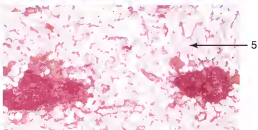
**Clinical Note:** Some bleeding disorders result from **thrombocytopenia**, a reduction in the number of circulating platelets. One cause of thrombocytopenia is **ineffective megakaryopoiesis** resulting from deficiencies of folic acid or vitamin B<sub>12</sub>.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 225.*

1. What is this organ?



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## THYMUS

1. Thymus
2. Thymic cortex
3. Thymic medulla
4. Connective tissue septa
5. Involved thymus of older individual

**Key Points:** The **thymus** is a bilateral organ in the mediastinum. The thymus is subdivided into irregularly sized lobes by connective tissue septa that extend from the surrounding **capsule**. Each lobe has a peripheral **cortex**, which is highly basophilic due to the presence of densely packed lymphocytes. The more central **medulla** of each lobe has a lower cell density and is less basophilic. The developing lymphocytes of the thymus (also called thymocytes) are almost exclusively T cells, and normally, lymphoid follicles are never present.

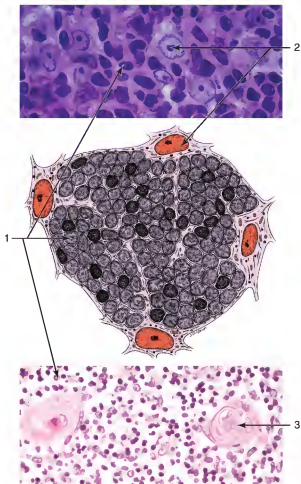
The thymus and the bone marrow, as the major sites of T- and B-cell precursors, respectively, are considered **primary or central lymphoid organs**. All other lymphoid organs, where lymphocytes are activated and proliferate, are classified as secondary or peripheral.

The thymus is the site of T-cell proliferation, differentiation, and the selective removal by apoptosis of lymphocytes that cannot interact with antigen-presenting cells and those that bind strongly when presented with endogenous proteins. T cells reacting to such "self-antigens" are a potential cause of autoimmune disorders and are removed as they develop in the thymus, the organ for the induction of central **self-tolerance**. More than 95% of the T cells arising by proliferation in the thymic cortex undergo apoptosis there; suitable lymphocytes move to the thymic medulla and leave the organ by crossing the endothelium of venules there.

The thymus is most active, largest, and best developed during childhood. After puberty, a process of **thymic involution** begins, with lymphoid tissue replaced by adipose tissue and few regions with lymphocytes remaining in older individuals.

**Clinical Note:** Failure of the third and fourth pharyngeal pouches to develop normally in the embryo and form the thymus leads to **DiGeorge syndrome**, characterized by **thymic hypoplasia** (or aplasia). Lacking epithelial reticular cells, such individuals cannot produce T lymphocytes properly and have severely depressed cell-mediated immunity.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 236-238.*



## THYMIC CORTEX AND MEDULLA

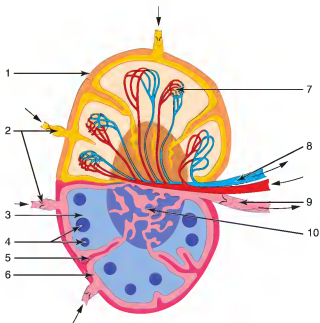
1. Lymphocytes
2. Epithelial reticular cells
3. Thymic (Hassall's) corpuscles

**Key Points:** Lymphocytes and macrophages in the thymic cortex and medulla are supported by a stroma composed largely of specialized **epithelial reticular cells** rather than connective tissue. Important features of epithelial reticular cells include the following:

- They are **keratin-rich** cells of epithelial origin, still firmly attached to one another by **junctional complexes**.
- These attached cells form branching strands of a **cytoreticulum** throughout the thymus to which lymphocytes become associated.
- They are derived from endoderm and ectoderm of the third and fourth **pharyngeal pouches and clefts**.
- In the thymic medulla, these cells form pale-staining, variously sized, concentrically layered aggregates called **thymic (Hassall's) corpuscles**, which are important landmarks distinguishing the thymus from other lymphoid organs.
- Several other **different types** of epithelial reticular cells are recognized that have various functions in different regions of the thymic cortex and medulla.
- Functions of the various types of epithelial reticular cells include:
  - **physical support and compartmentalization** of lymphocytes and macrophages within the cortex and medulla;
  - secretion of **thymosins, thymopoietin**, and various other factors important for T cell differentiation and lymphoid development;
  - formation of a **blood-thymus barrier** around vessels in the thymic cortex; and
  - formation of another **selective barrier** between the thymic cortex and the medulla.

**Clinical Note:** B cell follicles are typical of all other lymphoid organs but are only commonly found in the thymus if the patient has an **autoimmune disorder**. Tumors stemming from epithelial reticular cells, **thymomas**, are distinguishable from **lymphomas** by their relative lack of lymphocytes.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 236-238.*





## LYMPH NODE

1. Capsule
2. Afferent lymphatics
3. Cortex
4. Lymphoid follicles (nodules)
5. Trabecula of connective tissue
6. Subcapsular sinus
7. Microvasculature around follicles
8. Artery and vein
9. Efferent lymphatic
10. Medulla

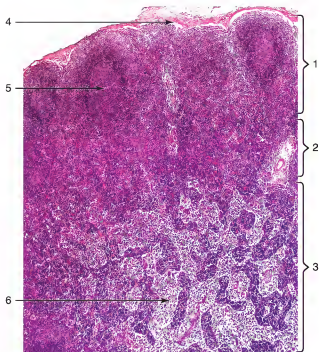
**Key Points:** Lymph nodes are encapsulated, bean-shaped structures, ranging from 1 to 20 mm in length, distributed along the lymphatic vasculature throughout the body. They are key sites for the interaction of antigen-presenting cells and lymphocytes and for the proliferation and differentiation of B cells and, therefore, are very important in humoral immunity. Major features of a lymph node include:

- connective tissue capsule and trabeculae;
- an **artery and a vein** entering only at the hilum on the concave side;
- an **efferent lymphatic**, also emerging at the hilum, that drains lymph from the organ;
- one or several **afferent lymphatics** entering on the side opposite the hilum;
- the **subcapsular sinus**, which receives lymph from the afferent lymphatics;
- a peripheral **cortex** normally containing **lymphoid follicles** or **nodules**; and
- a more central **medulla** lacking lymphoid nodules, but rich in B lymphocytes.

The stroma throughout a lymph node consists of a fine meshwork of reticulin fibers and is penetrated by lymphatic sinuses. This supportive reticulin meshwork is often shown stained black in silver-stained sections of lymph nodes.

**Clinical Note:** Neoplastic proliferation of lymphocytes, producing a malignant **lymphoma**, can occur in one or more lymph nodes. Such growth can completely obliterate the normal architecture of the node, converting it to an enlarged, encapsulated structure filled with disorganized lymphocytes.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 241 and 243-245.*



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## LYMPH NODE

1. Cortex
2. Paracortex
3. Medulla
4. Subcapsular sinus
5. Lymphoid follicle or nodule
6. Medullary sinus

**Key Points:** Between the **cortex** and the **medulla** of lymph nodes is a narrower and less well-defined region called the **paracortex** (or deep cortex). All three regions have a reticulin stroma and reticular cells. Special functions of the three regions are as follows:

The cortex:

- is the principal area where antigens in lymph entering the lymph node are processed by **antigen-presenting cells**, usually macrophages or dendritic cells, for presentation to B cells.
- It is also the principal area where the activated B cells undergo DNA rearrangement and proliferate clonally, forming the pale-staining **germinal centers** of **lymphoid follicles** or **nodules**.
- The **subcapsular sinus** of the cortex continues along the trabeculae, forming a branching network of sinuses leading to the efferent lymphatic.

The paracortex:

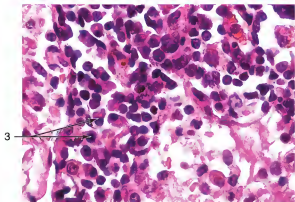
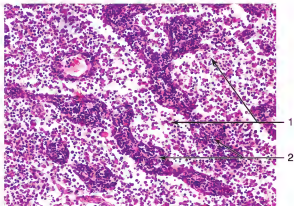
- **lacks lymphoid nodules** but contains some T lymphocytes; and
- contains specialized **high endothelial venules**, which provide another point of lymphocyte entry.

The medulla contains:

- **medullary sinuses** draining to the efferent lymphatic; and
- between the sinuses, **medullary cords** composed of reticular cells, lymphocytes, and plasma cells.

**Clinical Note:** **Metastatic cells** from a primary tumor can enter lymphatics and be carried to the subcapsular sinus of a nearby downstream lymph node, where growth of the cancer cells may continue. The presence of such tissue in sampled lymph nodes is a key indicator of metastasis.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 241 and 243-245.*



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## LYMPH NODE MEDULLA

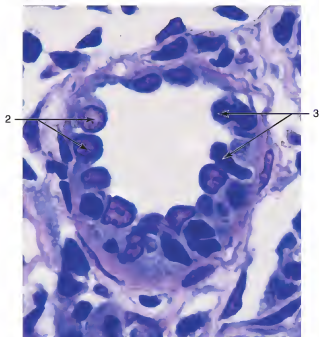
1. Medullary sinuses
2. Medullary cords
3. Plasma cells in medullary cord

**Key Points:** The **medullary regions** of lymph nodes do not typically contain lymphoid follicles and consist mainly of large **sinuses** that contain lymphocyte-rich lymph and are separated from each other by **medullary cords**. The cords contain various cells densely packed on the reticulin fibers, among which active **plasma cells** are prominent. Plasma cells are differentiated B lymphocytes specialized for the synthesis and secretion of the antibodies against the antigens that were presented to their precursor B cells. Compared to B lymphocytes, plasma cells have much more cytoplasm containing abundant rough endoplasmic reticulum and a large Golgi apparatus for antibody production. Lymph in the medullary sinuses leaves the lymph node via the efferent lymphatic and carries antibodies, lymphocytes, and some plasma cells to other locations.

**Clinical Note:** **Plasma cell neoplasia** involves proliferation of these cells still secreting immunoglobulin. The most common such disorder is **multiple myeloma**, in which neoplastic plasma cells lodge in the bone marrow, potentially effacing the hemopoietic tissue.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 241 and 243-245.*

1. What is this structure, located in the paracortex of lymph nodes?



14

## LYMPH NODE PARACORTEX

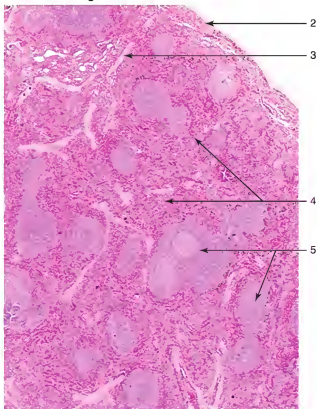
1. High endothelial venule (HEV)
2. Cuboidal cells of HEV
3. Lymphocytes crossing endothelium

**Key Points:** Venues passing through the paracortex from the microvasculature of the cortex to veins converging in the medulla have specialized endothelium that allows lymphocytes and antigen-presenting cell precursors to enter the paracortex directly from the blood. These are called **high endothelial venules** because the individual cells lining the lumen are more **cuboidal** rather than squamous in shape. Most lymphocytes enter lymph nodes in this manner, with proteins on their surfaces binding glycoprotein ligands on the luminal surface of the cuboidal endothelial cells, followed by their rapid migration between these cells into the surrounding stroma of the paracortex.

**Clinical Note:** Besides their normal presence in lymph nodes and other secondary lymphoid organs, high endothelial venules can develop in certain other organs that become sites for **chronic inflammatory disease**. Such venules apparently facilitate immigration of lymphocytes and other leukocytes in the synovium with rheumatoid arthritis or in the large intestine with ulcerative colitis.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 243-245.*

1. What is this organ?



14



## SPLEEN

1. Spleen
2. Capsule
3. Trabecula
4. Red pulp
5. White pulp

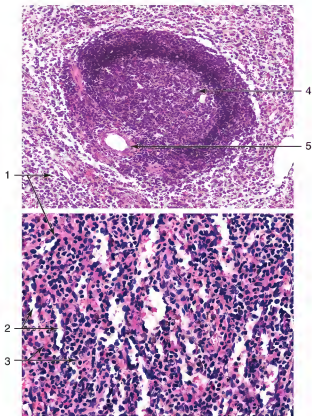
**Key Points:** The **spleen** is the largest secondary lymphoid organ and is the only such tissue also involved with blood filtration and removal of old erythrocytes. A connective tissue **capsule** extends numerous **trabeculae** carrying the major vascular branches. Between these trabeculae the **splenic pulp** consists of reticular tissue, with a meshwork of reticular cells and fibers loosely supporting an ever-changing population of lymphocytes, erythrocytes, and other blood cells.

In fresh, unstained sections of spleen, the pulp shows two types of tissues:

- **Red pulp** constitutes most of the spleen (>75%) and is the site of blood filtration and removal of effete, swollen, or rigid red blood cells.
- Scattered smaller regions of **white pulp** represent lymphoid tissue and consist mainly of lymphocytes for detection of blood-borne antigens. B cells often proliferate to form typical lymphoid follicles in these regions.

**Clinical Note:** Enlargement of the spleen, **splenomegaly**, can occur from a variety of causes, including lymphoma or other malignant growth, infections such as mononucleosis, or sickle cell disease and other types of anemia. The splenic capsule is relatively thin, and an enlarged spleen is susceptible to traumatic rupture, a potentially life-threatening occurrence due to loss of blood into the abdominal cavity. Such rupture may require prompt surgical removal of the spleen, **splenectomy**, after which most functions of the organ are carried out by other lymphoid organs, with erythrocyte removal occurring in the liver and bone marrow.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 245-248.*



## SPLENIC WHITE AND RED PULP

1. Red pulp
2. Splenic venous sinuses in red pulp
3. Splenic cords in red pulp
4. Lymphoid follicle in white pulp
5. Central arteriole with periarteriolar lymphoid sheath (PALS)

**Key Points:** The **white pulp** contains:

- **Central arterioles**, which branch into the splenic pulp from arteries in trabeculae
- Numerous T cells, which comprise most of the **periarteriolar lymphoid sheath (PALS)** that surrounds each central arteriole
- B cells, which may be stimulated to proliferate and form typical **lymphoid follicles**, in which case, the central arteriole and PALS are pushed eccentrically as the region of white pulp is greatly enlarged.

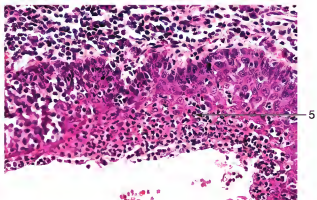
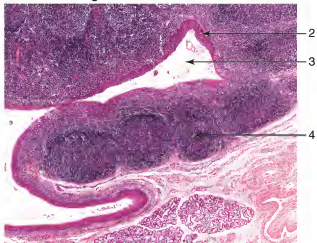
In the **red pulp**:

- Arterioles extend from the central arterioles and lead to capillaries and larger, unique **venous sinuses**.
- Blood flow here can take either of two routes:
  - **Closed circulation**, in which blood flows directly into the **venous sinuses**.
  - **Open circulation**, in which capillaries are open-ended and dump the blood into the **splenic cords**, the reticular tissue surrounding the venous sinuses. From the splenic cords, blood cells must reenter the circulation by transmigration across the wall of the sinuses. A discontinuous basement membrane and unique, elongated endothelial cells, often called **stave cells**, lining these sinuses allow rapid entry of the motile leukocytes. The thin, flexible erythrocytes reenter the circulation by slipping through the spaces between the stave cells. Swollen and inflexible red blood cells, typically those older than 120 days, cannot pass between stave cells and are removed by the numerous macrophages present in the surrounding cords.

**Clinical Note:** **Sickle cell disease** and other blood disorders that produce abnormally rigid or swollen erythrocytes can lead to **splenomegaly** as the cells accumulate in the red pulp more rapidly than they can be removed.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 245-248.*

1. What is this organ?



14

## TONSIL

1. Tonsil
2. Epithelium
3. Crypt
4. Lymphoid follicle
5. Lymphocytes in epithelium

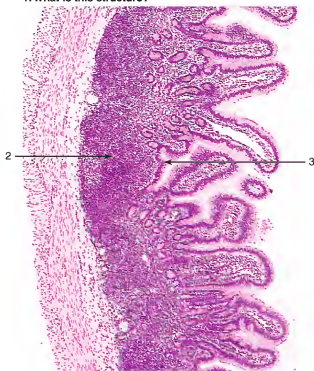
**Key Points:** Lymphocytes are common components of the mucosal lining of the digestive, respiratory, and urogenital tracts, where they provide immune defense against microorganisms crossing the surface epithelium. **Tonsils** are large components of this **mucosa-associated lymphoid tissue (MALT)**, located in the posterior oral cavity and pharynx.

Tonsils are covered on their outer surface by the stratified squamous **epithelium** of the mucosa and are encapsulated basally by connective tissue of the mucosa or submucosa. The epithelium is sometimes deeply folded into the lymphoid tissue, producing **crypts** where lymphocytes, neutrophils, and various microorganisms are normally found. The surface epithelium commonly contains lymphocytes and other white blood cells. Lacking afferent lymphatics, tonsils receive most lymphocytes and antigen-presenting cells via high endothelial venules. Lymphoid follicles are common in tonsils, which are drained by efferent lymphatics.

**Clinical Note:** Inflammation of the tonsils, **tonsillitis**, is more common in children than adults. Chronic inflammation of the pharyngeal lymphoid tissue and tonsils of children often produces hyperplasia and enlargement of the tonsils to form “**adenoids**,” which can obstruct the eustachian tube and lead to middle ear infections.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 238-243.*

1. What is this structure?



14

## PEYER'S PATCH

1. Peyer's patch
2. Lymphoid follicle
3. Epithelium with M cells

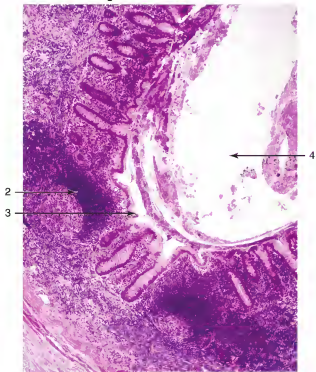
**Key Points:** Large aggregates of lymphoid tissue in the mucosa of the ileum are known as **Peyer's patches**. Each patch, which may be up to 3 cm in diameter, typically contains dozens of **lymphoid follicles** and may bulge into the lumen of the gut.

Peyer's patches are covered by simple columnar **epithelium** composed largely of enterocytes but also containing many unique epithelial cells called **M cells**, which form large intraepithelial pockets with transient populations of antigen-presenting cells and lymphocytes. The epithelium directly covering each accumulation of lymphoid tissue has a sieve-like basement membrane that allows easy access of leukocytes into the M cell pockets and between enterocytes. The antigenic material in the lumen of the ileum is sampled by these cells, and appropriate immune responses can follow rapidly.

**Clinical Note:** Inflammation of Peyer's patches is uncommon, but severe hyperplasia of this tissue can rarely produce **intussusception**, a medical condition in which the small intestine telescopes or invaginates upon itself, producing nausea and vomiting.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 240 and 275.*

1. What is this organ?



14



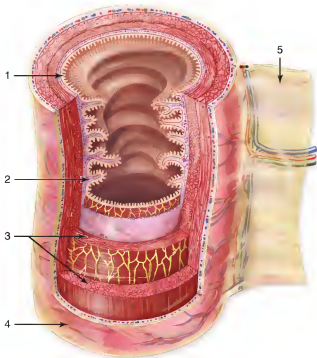
## APPENDIX

1. Appendix
2. Lymphoid follicle
3. Epithelium
4. Lumen

**Key Points:** A small amount of mucosa-associated lymphoid tissue (MALT) is present in the **appendix**, an 8- to 10-cm long structure blindly emerging from the cecum, near the junction of the small and large intestines. The wall of the appendix has the same layers as the intestinal wall, with the mucosa and submucosa typically filled with diffuse lymphocytes and **lymphoid follicles** covered only by the simple columnar **epithelium**. Besides serving as another source of lymphocytes, it has been suggested that the **lumen** of the appendix may serve as a reservoir from which the normal intestinal fauna can be rapidly reestablished when the large intestine is emptied thoroughly, such as during severe diarrhea.

**Clinical Note:** Acute **appendicitis** occurs most often when the opening to the appendix is obstructed by solid material or by lymphoid hyperplasia in the wall. Continued obstruction of the appendix opening may cause distention of the organ, loss of local blood flow, and ischemia. If not corrected or relieved by **appendectomy**, appendicitis can lead to necrosis and perforation of the wall, with leakage of infected contents into the abdominal cavity.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 274-280.*



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## DIGESTIVE TRACT OVERVIEW

1. Mucosa
2. Submucosa
3. Muscularis (circular and longitudinal layers)
4. Serosa
5. Mesentery

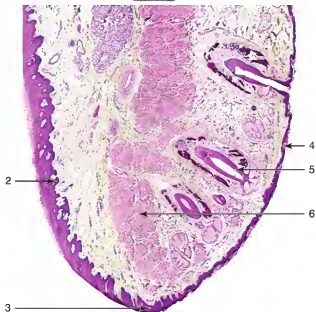
**Key Points:** Along its entire length, the digestive or gastrointestinal (GI) tract has four major layers, with their own subdivisions or special features:

- The innermost layer is the **mucosa**, with three concentric parts:
  - an **epithelial lining**, usually stratified squamous or simple columnar epithelium covering variously shaped folds of lamina propria,
  - underlying, well-vascularized connective tissue called the **lamina propria**, and
  - in some regions of the tract, a thin layer of smooth muscle called the **muscularis mucosae**.
- Surrounding the mucosa is the **submucosa** of somewhat denser connective tissue with larger blood vessels and the **submucosal plexus** of autonomic nerves.
- Surrounding the submucosa is the muscularis, a thick layer of smooth muscle usually separated as an internal sublayer with fibers disposed around the circumference of the tract and an external sublayer with fibers disposed longitudinally. Between these sublayers is the larger **myenteric plexus** of autonomic nerves.
- The outermost layer of the tract is a thin layer of connective tissue around the muscularis. This layer is called the **adventitia** when it merges with other connective tissue, such as that of the mediastinum surrounding the esophagus, but is termed the **serosa** when covered by mesothelium and suspended by **mesenteries** in the abdominal cavity.

**Clinical Note:** Along the entire GI tract, the mucosa forms a “thin red line” of defense against **potential pathogens** entering the body with ingested food and water. This includes the presence of abundant lymphocytes mostly in the lamina propria, a covering layer of mucus containing secretory immunoglobulin A antibodies and other antibacterial proteins, and various other cells of innate immunity.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 249-251.*

1. This is a section of \_\_\_\_\_.



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1. Lip
2. Oral mucosa
3. Transition zone
4. Skin
5. Hair follicle with sebaceous gland
6. Striated muscle

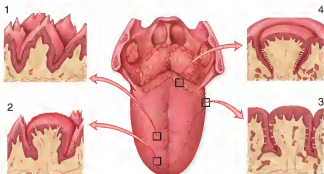
**Key Points:** The **lips** border the opening of the mouth and show the transition from keratinized epithelium of **skin** to the nonkeratinized epithelium lining the oral cavity. The surface of each lip thus includes three regions:

- A cutaneous part with **skin** having thin epidermis and usually showing **hair follicles** and **sebaceous glands**.
- The **oral mucosa**, or mucous membrane, consisting of a thick stratified squamous epithelium with downgrowths that interdigitate with connective tissue papillae from the underlying lamina propria. This epithelium is **nonkeratinized**, with the differentiating cells retaining their nuclei and having little cytoplasmic keratin, and is continuous with the ducts of **minor salivary glands**.
- Between these regions is a **transition zone** with thin, lightly keratinized stratified squamous epithelium over papillae of richly vascularized connective tissue. Blood in these vessels gives this area its red or vermilion color.

Between the connective tissue in the cutaneous region and the thick oral mucosa, lips show large fascicles of **striated muscle**, which allow the various movements of these structures.

**Clinical Note:** Infections of **herpes simplex virus 1** cause necrosis of infected epithelial cells, which frequently leads to vesicular or ulcerating lesions of the skin or mucous membrane on or near the lips. Inside the oral cavity, such lesions are called **canker sores**, and on the skin outside the mouth, they are usually called **cold sores** or **fever blisters**. Such lesions, often clustered and painful, occur when the body's immune defenses are weakened by emotional stress, fever, illness, or local skin damage and the virus, present in local nerves, can move to the epithelium.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 251-252.*



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## TONGUE AND LINGUAL PAPILLAE

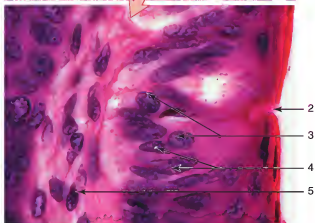
1. Filiform papilla
2. Fungiform papilla
3. Vallate papilla
4. Foliate papilla

**Key Points:** The tongue consists largely of striated muscle fascicles covered on its ventral surface by oral mucosa with nonkeratinized stratified squamous epithelium. Dorsally, the posterior third of the tongue is covered by the **lingual tonsils**, masses of lymphoid nodules separated by crypts, and the anterior two-thirds are covered by a mucosa whose surface is densely covered by **lingual papillae**. Four types of lingual papillae are recognized:

- **Filiform papillae**, the most numerous type, are **small, pointed projections** of keratinized epithelium that provide friction useful when the tongue moves food.
- **Fungiform papillae** are larger, less numerous, and scattered among the filiform papillae. They are **mushroom shaped** with cores of loose connective tissue covered by a nonkeratinized epithelium containing a few taste buds and other sensory receptors.
- **Foliate papillae**, also with nonkeratinized epithelium, consist of several parallel, **leaf-like ridges** on the lateral edges of the tongue. They are best developed in young children and usually disappear with age. The epithelium on the sides of each foliate papilla contains taste buds and is flushed continuously by **minor salivary glands** (of von Ebner) in the underlying lamina propria.
- **Vallate papillae** are very large dome-shaped papillae, and each is surrounded by a **moat-like cleft** or invagination of nonkeratinized epithelium with a large number of taste buds. These clefts are also flushed by von Ebner's salivary glands. A V-shaped line with 8 to 12 vallate papillae lies across the tongue just anterior to the lingual tonsils.

**Clinical Note:** All areas of the oral mucosa, including the surface of the tongue, can undergo **leukoplakia**, forming asymptomatic, thickened white patches where the epithelium has undergone hyperplasia and hyperkeratosis (excess keratinization). Leukoplakia can be caused by local irritations, such as tobacco use, and are considered premalignant lesions.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 252-253.*



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## TASTE BUDS

1. Taste buds
2. Taste pore
3. Nuclei of gustatory cells
4. Nuclei of supporting cells
5. Connective tissue

**Key Points:** Taste buds are epithelial structures located primarily in the mucosa on the sides of fungiform, foliate, and vallate papillae and on the soft palate, epiglottis, and posterior pharynx. Each taste bud is a barrel-shaped collection of tall epithelial cells embedded within the stratified squamous epithelium. An opening, or taste pore, at the epithelial surface leads into the structure which contains three major epithelial cell types:

- Elongated sensory or **gustatory cells** extend from the basal lamina to the taste pore. They have tight junctions and microvilli at their apical ends and basally have synaptic connections with sensory nerve fibers entering from the underlying **connective tissue**.
- Among the gustatory cells are **supporting cells** similar to the gustatory cells in many respects, but fewer, with more elongated nuclei, and lacking synapses with sensory nerves.
- Near the basal lamina are smaller **basal cells**, which are the stem cells for the other two cell types.

Membrane proteins on the apical ends of the gustatory cells react with chemical substances that mediate five basic tastes. Tastants for sweetness, bitterness, and umami (savory taste mediated by glutamate and related compounds) are detected by G-protein-linked receptors; salty and sour tastants are detected by ion channels.

**Clinical Note:** The rich and complex flavors of most food is perceived as much by the olfactory receptors in the nasal cavities as by the taste buds, as shown by the decreased ability to taste food in individuals with colds and **nasal congestion**. Individuals undergoing cancer chemotherapy commonly experience **reduced or altered taste perception**, which may be due to a cytotoxic effect on the dividing gustatory cell precursors or to the presence in saliva of certain antineoplastic drugs such as cisplatin.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 252 and 254.*



## TOOTH

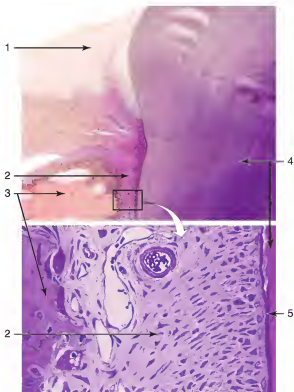
1. Crown
2. Neck
3. Root
4. Enamel
5. Gingiva
6. Dentin
7. Pulp cavity
8. Cementum
9. Periodontal ligament
10. Alveolar bone

**Key Points:** Despite differences in shape, all teeth show the following major features:

- Exposed above the gums or **gingiva**, is a **crown** composed of **enamel**, the hardest substance in the body, secreted by cells called ameloblasts in the developing tooth bud.
- Beneath this crown, the **neck** and **roots** of a tooth are composed largely of **dentin**, a hard substance secreted by cells called odontoblasts in the tooth bud and growing tooth.
- Dentin of the tooth roots is covered by a thin layer of **cementum**, similar to bone, produced and maintained by embedded cells called cementocytes.
- The tooth is attached to the **alveolar bone** of the jaw by the **periodontal ligament**, a fibrous connective tissue with many bundles of collagen fibers embedded in bone or cementum at each end.
- Dentin surrounds an internal **pulp cavity** containing connective tissue called dental pulp, which is well-vascularized and well-innervated via openings at the tip of each root.

**Clinical Note:** Enamel has a 96% composition of the mineral calcium hydroxyapatite, but it is not repaired after its production in the developing tooth. Bacteria form colonies in the surface grooves of enamel, especially when sugar is ingested frequently, and produce lactic acid, which demineralizes enamel locally, leading to the formation of **cavities (caries)** on the surface. Incorporation of fluoride makes enamel harder and more resistant to demineralization.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 254-259.*



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## PERIODONTIUM

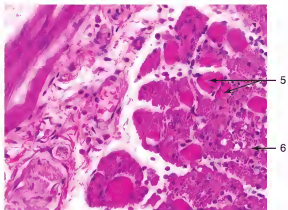
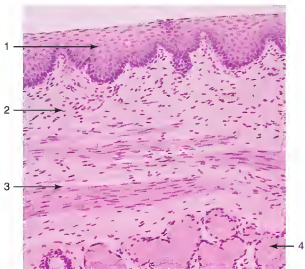
1. Stratified squamous epithelium of gingiva
2. Periodontal ligament
3. Alveolar bone
4. Dentin
5. Cementum

**Key Points:** The periodontium includes the supporting tissues of the tooth and the gingiva, or gums, the specialized oral mucosa surrounding each tooth. The gingiva has a thick, partly keratinized **stratified squamous epithelium** in which the basal layers are attached by a firm junction to **cementum** covering the **dentin** at the neck of each tooth. Above this junction is a very narrow crevice or sulcus between epithelium and tooth. Connective tissue beneath the gingival epithelium is dense, fibrous, and continuous with the periosteum of the **alveolar bone** in the jaw.

This connective tissue extends between the alveolar bone and the cementum covering the roots of the tooth as the **periodontal ligament**, which attaches the tooth to the bone. This ligament sheaths the roots of the tooth and contains small areas of vascularized connective tissue and a larger area with dense collagen fibers and aligned fibroblasts. Opposite ends of these fibers insert into cementum and the alveolar bone, supporting the tooth and firmly fixing it in place. Fibroblasts replace and reposition the collagen fibers continuously as alveolar bone is remodeled, allowing tooth movement during growth.

**Clinical Note:** Periodontal diseases include **gingivitis**, or inflammation of the gums, and **periodontitis**, both of which are caused most commonly by bacterial infections with poor oral hygiene. The inflammation of chronic periodontitis leads to weakening of the periodontal ligament and loosening of the teeth.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 258-260.*



## ESOPHAGUS

1. Stratified squamous epithelium
2. Lamina propria
3. Muscularis mucosae
4. Esophageal glands in submucosa
5. Striated muscle fibers in muscularis
6. Smooth muscle fibers in muscularis

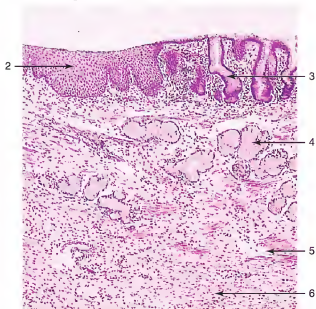
**Key Points:** The esophagus is a tube that gets food quickly from the oral cavity to the stomach. Here, the four layers have the following features:

- The **mucosa** is lined by **stratified squamous epithelium** and has a **lamina propria**, with lymphocytes and small mucous glands, and well-developed smooth muscle in the **muscularis mucosae**.
- The connective tissue of the **submucosa** contains large, mucous **esophageal glands** with ducts to the mucosal surface to lubricate food passing down the esophagus.
- The **muscularis** is very thick, with inner circular and outer longitudinal layers. The superior third of the muscularis contains mainly striated muscle involved in swallowing; the inferior third contains mainly smooth muscle, which moves food into the stomach by peristalsis; and the middle third seen in the figure is a transition zone containing both **striated and smooth muscle fibers**.
- The outermost layer is the dense connective tissue of an **adventitia** embedded in the tissue of the mediastinum.

**Clinical Note:** Esophageal cancer can involve either the mucosal epithelium, as **squamous cell carcinoma**, or cells of the mucous glands as **adenocarcinoma**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 259-260.*

1. What region of GI tract is seen here?



15



## ESOPHAGOGASTRIC JUNCTION

1. Esophagogastric junction
2. Stratified squamous epithelium of esophagus
3. Cardiac glands of stomach
4. Esophageal cardiac glands
5. Muscularis mucosae
6. Submucosa

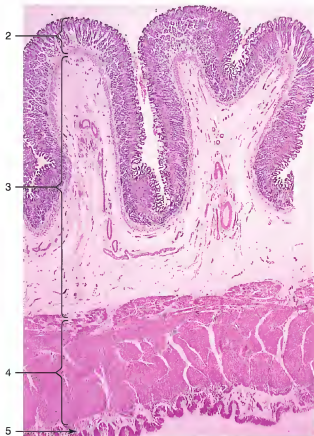
**Key Points:** After passing through the diaphragm, the esophagus joins with the cardiac region of the stomach. The major changes that occur histologically in the transition at this **esophagogastric junction** include the following:

- In the mucosa, there is an abrupt transition from **stratified squamous** to **simple columnar epithelium**. This lining of the stomach shows gastric pits, which here lead to mucus-secreting **cardiac glands**. The lamina propria of this region contains larger **esophageal cardiac glands** with ducts to the mucosal surface. The **muscularis mucosae** is relatively continuous through this region.
- The submucosa and muscularis show few histologic changes through this junction, although the inner circular layer of the **muscularis** forms a band, the **inferior esophageal sphincter**.
- In the abdominal cavity, the thin adventitial layer of the esophagus becomes a **serosa** covered by mesothelium.

**Clinical Note:** Mucus produced in the esophagus does little to protect the mucosa against acid that may regurgitate there from the stomach. This produces the painful sensation of **reflux esophagitis** or **heartburn**. An incompetent inferior esophageal sphincter may result in chronic heartburn, which can lead to erosion of the esophageal mucosa or **gastroesophageal reflux disease (GERD)**. GERD can also produce metaplastic changes in the stratified squamous epithelium of the esophageal mucosa, a condition termed **Barrett's esophagus**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 259 and 262.*

1. What are the large folds seen here called?



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## STOMACH

1. Rugae
2. Mucosa
3. Submucosa
4. Muscularis
5. Serosa

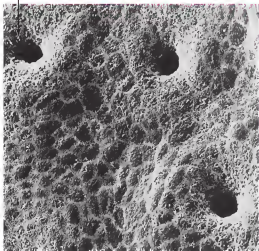
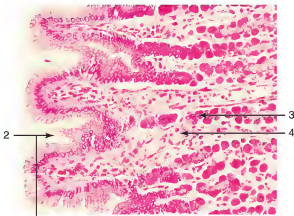
**Key Points:** In the stomach, food components are acidified and digestion of proteins begins. The stomach has **four regions**: an initial **cardia**; a dome-shaped **fundus** bulging superiorly; a very large **body**; and a funnel-shaped **pylorus** leading to the small intestine. Important features of the stomach's layers are:

- The **mucosa** and **submucosa** project into the lumen as large folds called **rugae**, which run lengthwise in the stomach.
- Loose connective tissue of the lamina propria is filled with invaginations of the surface simple columnar epithelium, which form branched tubular glands, each opening to the luminal surface via a gastric pore. In the cardiac and pyloric regions, these glands are uniformly mucus secreting and are called **cardiac** or **pyloric glands**. In the fundus and body, the glands contain a more diverse array of secretory cells and are called **gastric glands**.
- The muscularis mucosae is thick and separates the lamina propria from the submucosa.
- Smooth muscle of the **muscularis** is organized into **three layers** for efficient churning of food in the luminal contents to produce chyme. The external layer has fibers with a longitudinal orientation; the inner layer has circularly oriented fibers; and a middle layer has fibers oblique to those of the other layers.
- The outermost layer is a **serosa**.

**Clinical Note:** **Leiomyomas**, benign tumors of smooth muscle cells, are the most common tumor of the stomach. Studies of autopsy records have shown that the muscularis layers of stomach specimens have leiomyomas in 25 to 50% of the population over the age of 50. Leiomyomas range in size from very large to barely detectible masses.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 259 and 261-266.*

1. What region of the GI tract is shown here?



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## STOMACH MUCOSA

1. Stomach
2. Gastric pits
3. Gastric glands
4. Lamina propria

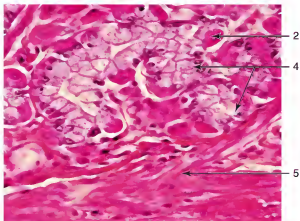
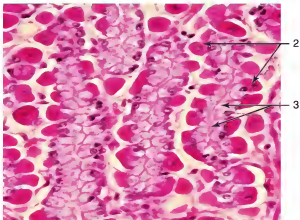
**Key Points:** The main features of the stomach mucosa include the following:

- The surface lining is composed of simple columnar epithelial cells that secrete an alkaline mucus.
- This epithelium invaginates into thousands of **gastric glands** that penetrate the full thickness of the **lamina propria**.
- The gastric glands are densely packed together, but each is surrounded by the highly vascular loose connective tissue of the lamina propria.
- The openings to these glands are called **gastric pores**, and the local epithelial cells resemble those of the luminal surface.
- The **muscularis mucosae** forms a well-defined sublayer near the ends of the gastric glands and extends many smooth muscle fibers into the lamina propria between these glands.

**Clinical Note:** Localized erosion of the gastric mucosa with focal necrosis is a condition called **acute hemorrhagic gastritis**, which is commonly associated with ingestion of aspirin or nonsteroidal anti-inflammatory drugs and excessive consumption of alcohol, all of which directly damage the gastric mucosa. This disorder may lead to the development of an **acute ulcer** if deeper layers become involved.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 261-264.*

1. Name these glands.



## GASTRIC GLANDS

1. Gastric glands
2. Parietal cells
3. Mucous neck cells and chief cells
4. Chief (peptic) cells
5. Muscularis mucosae

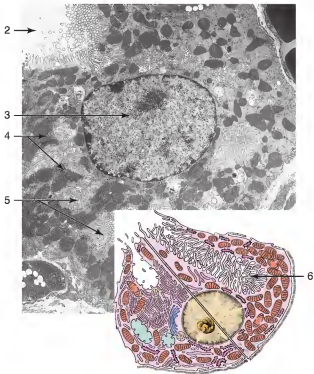
**Key Points:** The simple columnar epithelium of the **gastric glands** includes several specific secretory cells:

- At the upper region of the gland, near the gastric pore, are concentrated small columnar **mucous neck cells** secreting mucus having a pH more neutral than that of the gastric pores.
- Interspersed among these mucous cells are larger, more rounded, and more acidophilic cells called **parietal cells**, which produce the **hydrochloric acid (HCl)** needed to activate proteolytic enzymes in the stomach's lumen.
- Concentrated at the base of each gland, near the **muscularis mucosae**, are columnar cells that are smaller and less well-stained than the intervening parietal cells, called **chief cells** (also known as peptic or zymogenic cells). Chief cell cytoplasm has many granules containing inactive **pepsinogen**, the zymogen precursor for the protease pepsin.
- Much less numerous, difficult to detect routinely, and not shown here are **enteroendocrine cells**, which secrete various paracrine hormones modulating gastric functions.

**Clinical Note:** Autoimmunity against components of the parietal cells of gastric glands produces a condition called **atrophic gastritis**, which is often chronic and results in significant mucosal atrophy and loss of secretory function in the body and fundus of the stomach, but not the cardiac or pyloric regions because glands of these regions lack parietal cells.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 263-265.*

1. What cell is shown here?



15



## PARIETAL CELLS

1. Parietal cell
2. Lumen of gastric gland
3. Nucleus of parietal cell
4. Mitochondria
5. Microvilli in intracellular canaliculus
6. Intracellular canaliculus

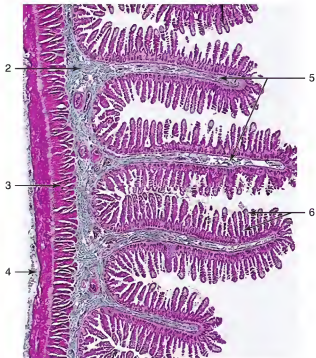
**Key Points:** Facts to note about **parietal cells** include the following:

- They produce **HCl** needed to activate digestive enzymes and the glycoprotein called **intrinsic factor** that is required for uptake of vitamin  $B_{12}$ .
- They are the **largest cells of gastric glands**, usually **round with central nuclei** and acidophilic cytoplasm due to the abundance of **mitochondria**.
- Ultrastructurally, parietal cells show the presence of invaginations called **intracellular canaliculi**, which elongate and develop numerous **microvilli** with active production of **HCl**.
- Using the enzyme carbonic anhydrase, an ATPase proton pump, and a  $Cl^-$  channel, the cells release  $H^+$  and  $Cl^-$ , which form **HCl** outside the cells.
- Parietal cell activity is stimulated by **gastrin** and **histamine** from nearby enteroendocrine cells and by parasympathetic nerves.

**Clinical Note:** For various reasons, parietal cells may fail to make sufficient quantities of intrinsic factor, which leads to a deficiency of vitamin  $B_{12}$  and **pernicious anemia**. This vitamin is a cofactor required for DNA synthesis, and its absence slows production of new erythrocytes and other cell types. Autoantibodies against intrinsic factor and other parietal cells proteins can also cause **atrophic gastritis**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 264-268.*

1. What region of the GI tract is shown here?



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## PLICAE CIRCULARES OF SMALL INTESTINE

1. Small intestine
2. Submucosa
3. Muscularis
4. Serosa
5. Plicae circulares
6. Villi

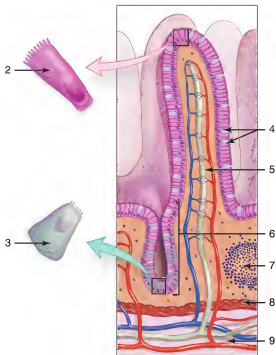
**Key Points:** The longest portion of the GI tract, the **small intestine** (small bowel), is the site where digestion is completed and the products of digestion are absorbed. It has three regions: the **duodenum**, the **jejunum**, and the **ileum**, which share most histological features.

- The **mucosa** and **submucosa** show distinct circumferential folds called **plicae circulares**, which are best developed in the jejunum and help to mix chyme and increase the absorptive surface area. The mucosa contains much mucosa-associated lymphoid tissue (MALT), with Peyer's patches in the ileum, and the submucosa contains the submucosal (Meissner) plexus of autonomic nerves, modulating activity of the muscularis mucosae and other mucosal functions.
- The surfaces of the plicae circulares and all other areas lining the small intestine lumen are covered with millions of finger-like projections called **villi**, composed of mucosa, which further increase the surface area.
- The **muscularis** is very well developed for peristaltic movement of material in the lumen. It has an internal circular layer and an external longitudinal layer, with the myenteric (Auerbach) plexus of autonomic nerves controlling peristalsis between them.
- The outermost layer is a **serosa** with attached mesenteries.

**Clinical Note:** Duodenal ulcers, like gastric ulcers, are painful erosive lesions that extend at least into the mucosa layer and often deeper. Such ulcers can actually occur anywhere between the lower esophagus and the jejunum, and their causes include infections with *Helicobacter pylori*, effects of nonsteroidal anti-inflammatory drugs, overproduction of HCl and pepsin, and underproduction of mucus.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 266-272.*

1. What structure is shown here?



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## VILLUS OF SMALL INTESTINE

1. Villus
2. Enterocyte
3. Paneth cell
4. Goblet cells
5. Lacteal
6. Intestinal gland (of Lieberkühn)
7. Lymphoid follicle in MALT
8. Muscularis mucosae
9. Vasculature in submucosa

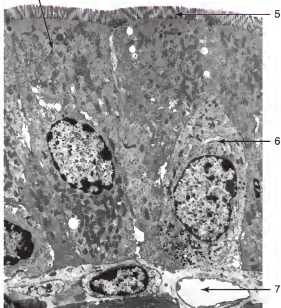
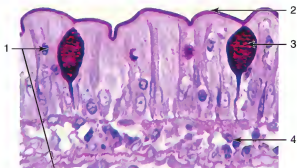
**Key Points:** Each villus of the small intestine lining includes the following basic features:

- A simple columnar epithelium covering composed mainly of **enterocytes** for food absorption and mucus-secreting **goblet cells**.
- A core of loose connective tissue that is part of the lamina propria.
- This connective tissue contains **microvasculature** extending from the underlying submucosa and a lymphatic capillary called a **lacteal**, for transport of absorbed lipid.
- Lymphocytes and **lymphoid follicles** are common in all areas of the lamina propria.
- At the base of each villus are a few short, tubular **intestinal glands (of Lieberkühn)**.
- The epithelial lining of these glands is continuous with that covering the villus and consists of the stem cells and undifferentiated precursors for enterocytes and goblet cells. Another major cell type of the glands/crypts is a secretory cell called the **Paneth cell**.

Immediately below the intestinal glands is the **muscularis mucosae**, which forms the lower boundary of the mucosa and includes smooth muscle fibers that extend into each villus.

**Clinical Note:** An **inflammatory bowel disease** occurring mainly in the small intestine is **Crohn disease**, in which excessive lymphocyte activity and inflammation occur transmurally in any or all layers of the wall, producing localized bleeding, malabsorption, and abdominal pain.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 266-272.*



## EPITHELIAL CELLS OF VILLI

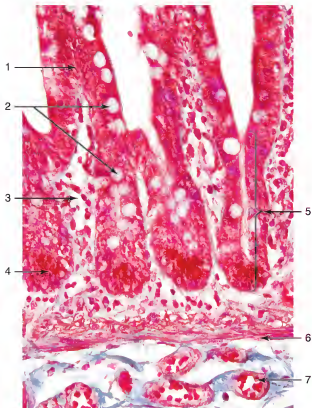
1. Enterocytes
2. Striated border of enterocytes
3. Goblet cell
4. Lamina propria
5. Microvilli of striated border
6. Enteroendocrine cell
7. Capillary in lamina propria

**Key Points:** Each villus is covered by a simple columnar epithelium composed mainly of **three cell types**:

- The most abundant cells, the **enterocytes**, are tall cells specialized for absorption of the nutritive breakdown products of food. The area of the apical cell surface across which absorption occurs is greatly increased by closely packed, uniform **microvilli**, each 1  $\mu\text{m}$  tall, which may be seen in light microscope preparations as the cells' apical brush or **striated border**. Transmembrane glycoproteins projecting from the microvilli form **glycocalyx** that also contains enzymes coupling the final steps of digestion with molecular uptake by the enterocytes. Products of digestion undergo **transcytosis** and are released from the basolateral membranes of the enterocytes for uptake by **capillaries** or **lacteals** in the **lamina propria**.
- Numerous **goblet cells** interspersed among the enterocytes secrete mucus, which contributes to the layer of this substance covering the intestinal mucosa. Goblet cells stain poorly with hematoxylin and eosin, but stain well with certain common histochemical procedures.
- Less numerous **enteroendocrine cells** are typically cuboidal, are difficult to see by light microscopy without special staining, and secrete paracrine factors into the lamina propria, although secretion into the lumen may also occur.

**Clinical Note:** **Celiac disease (celiac sprue)** is a disorder of the small intestinal mucosa that causes **malabsorption** and can lead to damage or destruction of villi. The cause of celiac disease is an immune reaction against gluten, a protein in wheat flour. The resulting inflammatory reaction affects the enterocytes, leading to malabsorption.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 268-273.*





## INTESTINAL GLANDS (CRYPTS OF LIEBERKÜHN)

1. Villus
2. Goblet cells
3. Lamina propria
4. Paneth cells
5. Intestinal gland or crypt
6. Muscularis mucosae
7. Microvasculature in submucosa

**Key Points:** The **intestinal glands** (or crypts of Lieberkühn) are short tubular invaginations at the base of each intestinal villus. Their lining is a simple columnar epithelium containing:

- **stem cells** for all the cells of the villus and the gland itself;
- **transit-amplifying cells** committed to become **enterocytes**, **goblet cells**, **enteroendocrine cells**, and **Paneth cells**; and
- **Paneth cells**, located at the base of each intestinal gland, with bright acidophilic granules for secretion of antibacterial peptides.

Below the intestinal glands is the **muscularis mucosae**, separating connective tissue of the **lamina propria** from that of the **submucosa**.

**Clinical Note:** Paneth cells are key components of the small intestine's **innate immune defense**, protecting the stem and progenitor cells by preventing local overgrowth of intestinal bacteria in the intestinal gland niche. Paneth cells secrete nonspecific antimicrobial proteins, including lysozyme and various **defensins**, which become concentrated in mucus and contribute to the **mucosal defense against enteric pathogens**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 268-271.*



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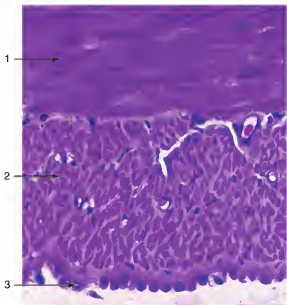
## DUODENAL (BRUNNER'S) MUCOUS GLANDS

1. Villi
2. Intestinal crypts or glands
3. Duodenal (Brunner's) mucous glands
4. Duct of duodenal gland
5. Muscularis mucosae

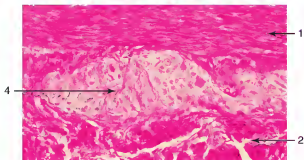
**Key Points:** The **submucosa** of the small intestinal duodenum contains many large **duodenal mucous glands**, also called Brunner's glands, with **ducts** extending through the **muscularis mucosa** and **lamina propria** to the intestinal lumen. Such large mucous glands are not found elsewhere in the small intestine. Mucous cells of these glands copiously produce mucus containing bicarbonate ions, which helps neutralize the HCl entering the duodenum from the stomach.

**Clinical Note:** The alkaline mucus of the duodenal glands is a major element protecting the mucosa against the formation of **duodenal ulcers**, which are most commonly **peptic ulcers** produced by the action of digestive proteases on the mucosa. The inflammation occurring in either **gastritis** or **duodenitis** usually causes **duodenal gland hyperplasia** and increased mucus production.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 269, 271, and 276.*



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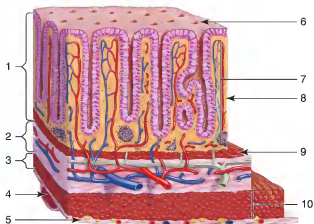
## SMALL INTESTINE MUSCULARIS

1. Internal layer of muscularis
2. External layer of muscularis
3. Serosa
4. Ganglion of myenteric plexus

**Key Points:** The two-layered **muscularis** of the small intestine is relatively thin but well-developed for continuous peristalsis, which mixes chyme entering the duodenum from the stomach with digestive juices from the pancreas and gallbladder and moves the mixture along the intestine. Between the **internal circular layer** of smooth muscle and the **external longitudinal layer** is the extensive **myenteric (Auerbach) plexus** of autonomic nerves, with their cell bodies in distinct **ganglia**. The myenteric plexus helps control peristaltic activity of the muscularis and is also interconnected with the submucosal (Meissner) plexus of autonomic nerves. Both nerve networks are part of the enteric nervous system present along the entire length of the GI tract. The muscularis is covered by a thin **serosa**.

**Clinical Note:** Medical problems involving the myenteric plexus and muscularis lead to **motility disorders**, which are most common as swallowing difficulties caused by loss of ganglionic neurons in the lower esophagus. Rarely, severe inflammation of the myenteric plexus in the ileum or large intestine can reduce movement of feces and cause constipation and **intestinal pseudo-obstruction**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 271, 272 and 277.*



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## LARGE INTESTINE

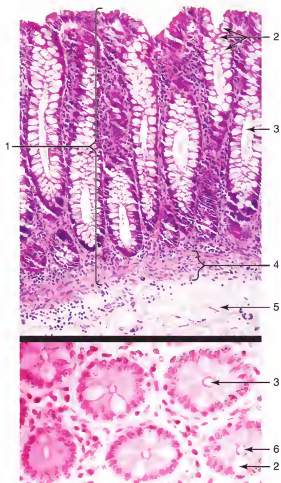
1. Mucosa
2. Submucosa
3. Muscularis
4. Taenia coli (external layer of muscularis)
5. Serosa
6. Opening to an intestinal gland
7. Intestinal gland
8. Lamina propria
9. Muscularis mucosae
10. Internal layer of muscularis

**Key Points:** At the end of the ileum, the GI tract undergoes an abrupt change in structure from the small to the **large intestine**. The latter has three major regions: a short **cecum**; a long **colon** with ascending, transverse, descending, and sigmoid portions; and the **rectum**. All three regions are similar histologically, with the following usual four layers:

- The **mucosa** contains many closely packed simple tubular **intestinal glands**, each with an **opening to the lumen** of the bowel, lined by a simple columnar epithelium. Each gland is surrounded by the loose connective tissue of **lamina propria**, with MALT. Near the bases of these glands is the **muscularis mucosae**.
- The **submucosa** is the site of larger blood vessels.
- The two-layered, peristaltic **muscularis** includes a **circular internal layer** and the myenteric (Auerbach) plexus, but unlike that in other regions of GI tract, the muscularis here has its external, longitudinal layer of smooth muscle disposed as three separate bands of tissue, called the **taeniae coli**.
- The outer layer is a **serosa**, with mesenteries.

**Clinical Note:** Herniation or outpocketing of the mucosa and submucosa of the colon can occur between the taeniae coli, forming bulges (diverticula) and a condition called **diverticulosis**. This disorder can occur if the colon wall is structurally defective or as a result of high intraluminal pressure or **constipation**. Fecal material can become immobilized in the diverticula and cause localized inflammation or **diverticulitis**.

See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 272, 274, and 278-279.



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## GLANDS OF LARGE INTESTINE

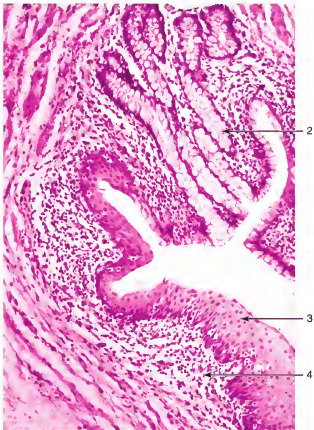
1. Mucosa
2. Goblet cells
3. Lumen of intestinal gland
4. Muscularis mucosae
5. Submucosa
6. Colonocytes

**Key Points:** The epithelium of the tubular **intestinal glands** is continuous with the surface lining of the large intestine and consists mainly of columnar cells with basal nuclei—**goblet cells** and **colonocytes**, which are absorptive cells with short microvilli at their apical ends and which remove most of the water from feces. The glands are each surrounded by lamina propria connective tissue, which extends to the **muscularis mucosae**. Diffuse lymphocytes and lymphoid follicles are typically abundant in both the **mucosa** and **submucosa**.

**Clinical Note:** **Colorectal cancer**, the second most common type of cancer in the United States, is an **adenocarcinoma** that develops from **benign adenomatous polyps** in the mucosal epithelium. Such polyps usually occur in epithelium of the rectum, sigmoid colon, or distal descending colon and are more common in individuals with low-fiber diets, which reduce the bulk of fecal material and consequently prolong contact of the mucosa lining with toxins in feces. Screens for colorectal cancer include **sigmoidoscopy** or **colonoscopy** to see polyps and tests for **fecal occult blood** resulting from mucosal bleeding as an adenocarcinoma invades more deeply into the mucosa.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 272, 274, and 278-279.*

1. What region of the GI tract is shown here?



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## RECTOANAL JUNCTION

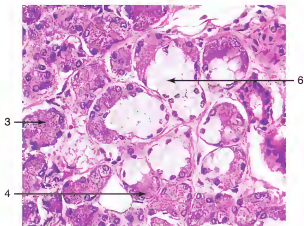
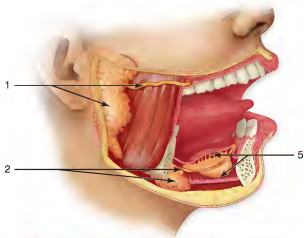
1. Rectoanal junction
2. Tubular glands of rectal mucosa
3. Stratified squamous epithelium of anal canal
4. Lamina propria with MALT

**Key Points:** At the **rectoanal junction**, the mucosal epithelium shifts abruptly from rectal simple columnar epithelium with **tubular glands** to the **stratified squamous epithelium** lining the anal canal and continuous with the epidermis of adjacent skin. The underlying **lamina propria** at this junction typically contains abundant lymphocytes and MALT.

The muscularis of this region is thickened as the internal anal sphincter. A more distal external anal sphincter composed of striated muscle relaxes to allow defecation.

**Clinical Note:** Swollen blood vessels in the mucosa or submucosa of the rectum or anal canal can cause a painful disorder called **hemorrhoids**. This common condition typically results from a low-fiber diet, constipation, prolonged sitting, or straining at defecation, conditions that produce increased pressure on these blood vessels.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 280.*



## SALIVARY GLANDS

1. Parotid gland and duct
2. Submandibular gland and duct
3. Serous acinus
4. Serous demilune
5. Sublingual gland and ducts
6. Mucous tubule

**Key Points:** Most saliva is secreted by three bilateral sets of **major salivary glands**:

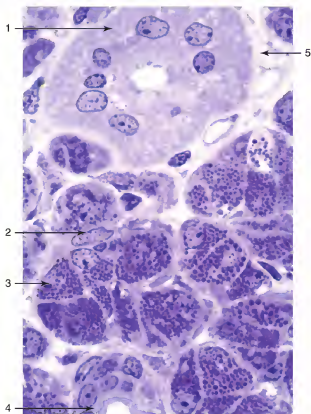
- The largest, the **parotid glands**, consist entirely of serous acini secretory units producing a watery secretion rich in amylase and other proteins.
- The **sublingual glands** contain mixed serous and mucous secretory units, although mucous cells predominate, producing mucus-rich saliva, with several small ducts opening under the tongue.
- The **submandibular glands**, below the body of the mandible, produce about 60% of the saliva and are also mixed serous and mucous glands, with serous cells predominating.

The submandibular glands (shown in the figure histologically) are branched tubuloacinar glands, with many **serous acini** and elongated **mucous tubules**. Groups of serous cells in mixed glands often appear as crescent-shaped extensions called **serous demilunes**. Both types of secretory units include flattened epithelial cells called **myoepithelial cells**, whose contractile processes surround the acinus and facilitate movement of the secretion into the duct system.

Each secretory unit is drained by a small intercalated duct. These are continuous with larger striated ducts, which merge into the still larger **excretory ducts** to the oral cavity.

**Clinical Note:** **Bilateral enlargement** of the major salivary glands may indicate infection by a virus such as the **mumps virus**, which usually affects the parotid glands. **Unilateral enlargement** of the glands is more likely due to another cause of inflammation, cyst formation, or neoplastic growth.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 281-285.*



## PAROTID SALIVARY GLAND

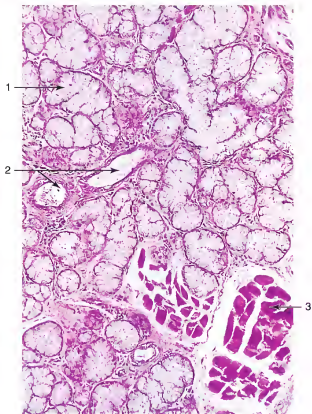
1. Striated duct
2. Nucleus of myoepithelial cell
3. Serous acinus
4. Intercalated duct
5. Connective tissue

**Key Points:** Parotid glands are entirely serous, with the secretory cells of the acini filled apically with well-stained granules. Immediately surrounding these cells are processes of a few **myoepithelial cells**, cells that are also inside the basal lamina and whose contractions help expel secretions into the ducts. The lumen of each **serous acinus** is very small.

Myoepithelial cells may also be present in the simple cuboidal epithelium of the small **intercalated ducts**, which directly drain the acini. These ducts drain into larger **striated ducts** composed of simple columnar epithelium and surrounded by a small amount of **connective tissue**. The columnar cells of these ducts have centrally located nuclei, with their basal ends having many infoldings of the cell membrane lined by mitochondria and giving this region a faintly “striated” appearance. The mitochondria and the increased surface area provided by the membrane folds are involved in uptake of  $\text{Na}^+$  ions from the secreted fluid, causing saliva normally to be slightly hypotonic, with a  $\text{Na}^+$  concentration only one-tenth that of blood plasma.

**Clinical Note:** Various components in saliva, including calcium, phosphate, and fluoride ions (where available), as well as the antibacterial enzyme lysozyme, help maintain the teeth and protect them from erosion by acidic ions from bacteria. Chronically insufficient saliva production, or **dry mouth**, can lead to tooth caries and other dental problems.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 282-285.*



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## SUBLINGUAL SALIVARY GLAND

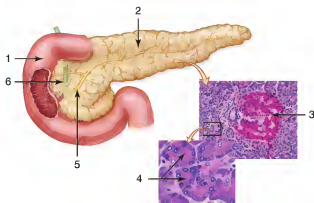
1. Mucous tubule
2. Intralobular duct
3. Striated muscle

**Key points:** The small sublingual glands are considered mixed glands but contain primarily **mucous secretory units**, which are mainly elongated as tubules. The scarcity of serous acini or serous demilunes is characteristic of the sublingual gland and distinguishes it from the submandibular gland. Like goblet cells, the cells of mucous glands are typically poorly stained due to the loss of secretory granules during tissue processing.

All intercalated, striated, and excretory ducts in the sublingual glands are short and, therefore, more difficult to locate in sections. The larger **intralobular ducts**, like the other large ducts, are surrounded by connective tissue, and **striated muscle** below the tongue may also be present.

**Clinical Note:** Dryness of the mouth, also called **xerostomia**, can be caused by various factors affecting the major salivary glands, including **mumps** or tissue irradiation, and is a normal adverse effect of several drugs, such as **antihistamines**. **Sialorrhea**, or increased production of saliva, is associated with **oral cavity inflammation**, **nausea**, and infection by the **rabies virus**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 282-285.*



## PANCREAS

1. Duodenum
2. Pancreas
3. Pancreatic islet (of Langerhans)
4. Pancreatic acini
5. Main pancreatic duct
6. Common bile duct

**Key Points:** The **pancreas** is a retroperitoneal organ in the superior left quadrant of the abdominal cavity. This gland has a very thin connective tissue capsule, fine septa, and a sparse stroma, with the parenchyma consisting mainly of exocrine cells secreting digestive enzymes and the less abundant **islets** (of Langerhans) containing insulin-producing cells (discussed later with other endocrine tissues). The secretion from most of the **pancreatic acini** drains into the **main pancreatic duct**, which leaves the pancreas and merges with the **common bile duct** at the hepatopancreatic ampulla before entering the **duodenum**.

Digestive enzymes secreted by the pancreatic acini include:

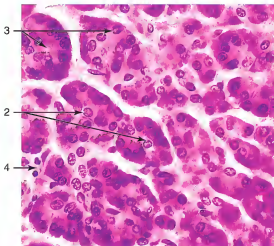
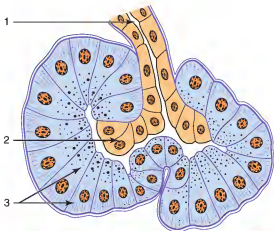
- inactive, proenzyme forms of the proteases **trypsin**, **chymotrypsin**, **elastase**, and **carboxypeptidase** (trypsin is activated in the duodenum where it in turn activates the other pancreatic proteases);
- various **lipases** producing mainly free fatty acids;
- **$\alpha$ -amylase** for breakdown of carbohydrates; and
- **nucleases** (both deoxyribonuclease and ribonuclease).

In the duodenum, these pancreatic enzymes serve as the major components for digestion of the macromolecules of food.

**Clinical Note:** **Pancreatic cancer**, which is usually an adenocarcinoma of the duct cells, can arise anywhere in the pancreas, but usually occurs in the head of the organ near the duodenum. This is one of the most lethal forms of cancer because it is rarely detected in its early stages. The tumor is usually asymptomatic until growth and metastasis are well advanced. Metastasis may be facilitated by the relatively sparse connective tissue surrounding the ducts and vasculature and forming the thin capsule of the pancreas.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 285-286.*

(Right bottom image used with permission from Carolina Biologic Supply Company/Phototake; Left bottom image used with permission from Carolina Biologic Supply Company/Visuals Unlimited.)



## EXOCRINE PANCREAS

1. Intercalated duct
2. Centroacinar cells
3. Acinar cells
4. Connective tissue

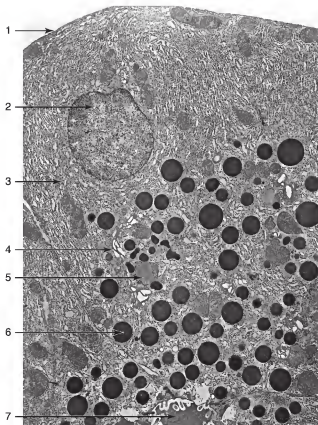
**Key Points:** Exocrine cells of the pancreas, often called **acinar cells**, are serous, pyramidal, and located within the numerous pancreatic acini. These acini have very small lumens, lack myoepithelial cells, and are surrounded by only sparse **connective tissue**. Near the lumen, the apical ends of the exocrine cells are filled with acidophilic secretory granules; the basal end of each cell is much more basophilic, containing abundant rough endoplasmic reticulum (RER) and the nucleus.

Each pancreatic acinus is drained by a short **intercalated duct** of simple cuboidal epithelium and a small diameter. The initial portion of each intercalated duct is inserted into the lumen of the acinus and its more pale-stained cells appear there as **centroacinar cells**. These cells and the adjacent cells of the intercalated ducts secrete large amounts of water rich in  $\text{HCO}_3^-$  ions. This alkaline fluid hydrates and transports the enzymes secreted by the acinar cells and, in the duodenum, serves to neutralize the strongly acidic chyme entering from the stomach to a pH optimal for activity of the pancreatic enzymes.

The intercalated ducts drain into larger intralobular ducts, with taller cells and more connective tissue. Intralobular ducts merge to form larger interlobular ducts located in the septa of the gland and draining into the main and accessory pancreatic ducts. None of these ducts are striated.

**Clinical Note:** **Acute pancreatitis** is an inflammatory condition of the exocrine pancreas resulting from injury to the acini and has the potential for leakage and activation of the digestive enzymes. The initiating damage may be due to an obstruction in the ducts, trauma, reflux of bile or the duodenal contents into the pancreas, or other causes. **Chronic pancreatitis** can involve chronic inflammation producing progressive fibrosis and loss of functional pancreatic tissue.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 286-287.*



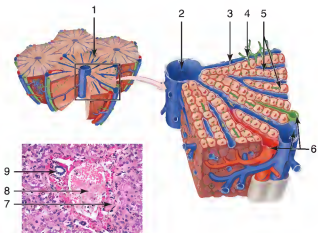
## PANCREATIC ACINAR CELL ULTRASTRUCTURE

1. Basal lamina
2. Nucleus
3. Rough endoplasmic reticulum (RER)
4. Golgi apparatus
5. Condensing vacuole
6. Secretory granule
7. Lumen of acinus

**Key Points:** The pyramidal cells that make up the pancreatic acini are classic exocrine secretory cells with basal-apical polarity. The wide basal end of each cell is associated with the **basal lamina** surrounding the acinus and contains the spherical, euchromatic **nucleus**. Cytoplasm in this part of the cell contains mainly profuse **RER** and mitochondria. On the apical side of the nucleus is a large **Golgi apparatus** from which emerge numerous large **condensing vacuoles**, which mature quickly as denser **secretory granules** containing the digestive enzymes. Such vesicles fill the narrow apical end of the cell, waiting on signals for exocytosis into the small **lumen** in the center of the acinus.

**Clinical Note:** Kwashiorkor, a syndrome resulting from a diet chronically deficient in protein but with adequate carbohydrates, is characterized by pancreatic changes that include loss of activity and atrophy in the exocrine cells. Characteristic features of the disorder also include histologic changes in the liver cells and atrophy of villi in the small intestine.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 286-288.*





## LIVER

1. Hepatic lobule
2. Central venule
3. Sinusoid
4. Bile canaliculi
5. Hepatocytes
6. Portal triad
7. Branch of hepatic artery
8. Branch of portal vein
9. Bile ductule

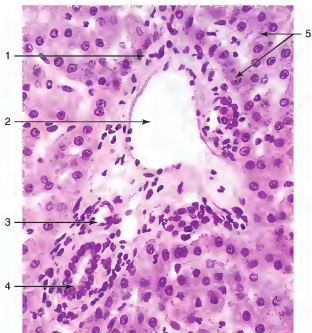
**Key Points:** The liver has large left and right lobes and acts as an interface between molecules absorbed in the digestive system and the blood. It has a thin connective tissue capsule and only a delicate stroma of reticular fibers except around the blood vessels. **Hepatocytes**, the main parenchymal cells of the liver, are epithelial cells present in interconnected plates that make up thousands of small **hepatic lobules**. Each lobule has the following parts, all supported by reticular fibers:

- A **central vein** or **venule**
- Irregular plates of **hepatocytes** that run from the lobule's periphery to the central vein
- **Sinusoids** between the plates of hepatocytes that enter the central venule from all directions
- **Bile canaliculi**, which are interconnected, channel-like spaces between the hepatocytes where bile is secreted and transported

At the periphery of each hepatic lobule are three to six portal areas, each containing a set of three small vessels termed the **portal triad**, which consists of a **branch of the portal vein**, a **branch of the hepatic artery**, and a **bile ductule**.

**Clinical Note:** After **partial hepatectomy** in rats, the remaining hepatocytes proliferate and are reorganized into new, enlarged hepatic lobules, and the original mass of the organ may be restored. A similar process of **liver regeneration** can restore normal liver volume following **split liver transplantation** of either the left or right lobe from living donors to human patients with acute or chronic **hepatic failure**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 287-289.*



## HEPATIC PORTAL AREA

1. Connective tissue
2. Portal venule
3. Hepatic arteriole
4. Bile ductule
5. Hepatocytes

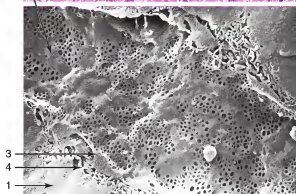
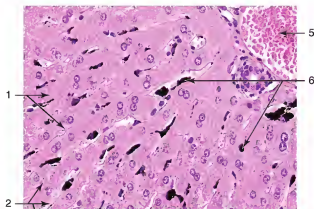
**Key Points:** Three to six **portal areas**, or portal tracts, with small amounts of dense irregular **connective tissue** are situated at the periphery of each hepatic lobule. Each of these areas contains the following structures:

- a venule **branch of the portal vein** carrying nutrient-rich blood to the sinusoids;
- an arteriole **branch of the hepatic artery** carrying  $O_2$ -rich blood to the sinusoids; and
- a **bile ductule** carrying bile transported there by the canaliculi.

These three structures make up the so-called portal triad. Most portal areas also contain a lymphatic capillary.

**Clinical Note:** In the normal liver, most dense connective tissue is found only in the portal areas, surrounding the blood vessels and bile ductule. In liver **cirrhosis**, which occurs late in **chronic liver disease**, fibroblast proliferation and fibrosis occur beyond the portal areas. The excessive connective tissue may disrupt the normal hepatic architecture and surround nodules of hepatocytes, interfering with liver function.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 287-291.*



## HEPATIC SINUSOIDS

1. Hepatocytes
2. Sinusoids
3. Endothelial cell
4. Perisinusoidal space (of Disse)
5. Portal venule
6. Stellate macrophages with ingested India ink

**Key Points:** In each hepatic lobule, **sinusoids** connect the branching **portal venules** and hepatic arterioles in the portal areas with the central vein. Each irregular, dilated sinusoid has the following characteristics:

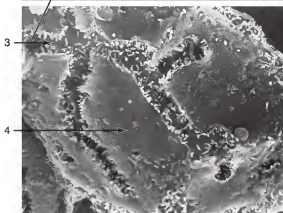
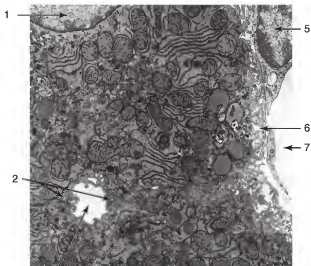
- It is lined by an endothelium with a sparse, discontinuous basement membrane and a discontinuous layer of fenestrated **endothelial cells**.
- The endothelium is surrounded by a fine network of reticulin fibers but no dense connective tissue.
- This endothelium and the adjacent plate of **hepatocytes** are separated by a very thin **perisinusoidal space** (of Disse) that contains plasma entering through the discontinuities from the sinusoidal blood. Microvilli from the hepatocyte surface are also abundant here.
- Monocyte-derived **stellate macrophages**, also known as Kupffer cells, reside in and around the sinusoids and remove blood-borne debris, nonfunctional erythrocytes, and other material.

O<sub>2</sub>-rich blood from the hepatic arterioles mixes with nutrient-rich blood from the portal venules in the first part of each sinusoid. Near the central vein at the last part of the sinusoids, the blood now has more CO<sub>2</sub> and contains newly made proteins synthesized and secreted by the hepatocytes, such as clotting factors and albumin.

**Clinical Note:** The **fibrosis** characteristic of **cirrhosis** produces collagen and other connective tissue components that fill the perisinusoidal space and interfere with metabolic exchange between the hepatocytes and the sinusoids. Blockage of hepatocyte secretion into the blood can result in **clotting disorders**, **hypoalbuminemia**, and other medical problems.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 287-291.*

(Bottom image used with permission from Eddie Wisse, Electron Microscopy Unit, Department of Pathology, University of Maastricht, The Netherlands.)



## ULTRASTRUCTURE OF BILE CANALICULI AND PERISINUSOIDAL SPACE

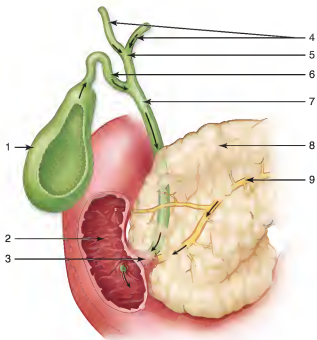
1. Nucleus of hepatocyte
2. Junctional complexes at bile canaliculus
3. Bile canaliculi
4. Hepatocyte
5. Nucleus of endothelial cell
6. Perisinusoidal space (of Disse)
7. Sinusoid lumen

**Key Points:** Transmission electron microscopy (TEM) shows that **hepatocytes** contain numerous mitochondria, glycogen granules, and much smooth endoplasmic reticulum which contains enzymes for detoxification of ingested compounds, as well as RER, lipid droplets, and other cytoplasmic structures. The hepatocyte surface at the **perisinusoidal space** (of Disse) is seen to have many irregular microvilli projecting into this space and providing a great surface area for metabolic exchange between the cells and blood entering there from the **sinusoid lumen**.

**Bile canaliculi** are seen by both TEM and scanning electron microscopy to be elongated spaces between adjacent hepatocytes that are firmly joined by **junctional complexes** along these spaces. Into these canaliculi, the hepatocytes release **bile**, an exocrine secretion of water containing bile salts and bilirubin with heme from degraded erythrocytes. These canaliculi are continuous across the surfaces of many hepatocytes, carrying bile toward a bile ductule in the portal area. The flow of bile in a hepatic lobule is therefore opposite to that of the blood flowing in the sinusoids toward the central vein.

**Clinical Note:** **Jaundice**, the yellowing of the skin or sclerae of the eyeballs due to the presence of bilirubin in the circulating blood, can result when bile canaliculi are disrupted by hepatocyte loss during **viral hepatitis** or by **cirrhosis**, which lead to release of bile into the blood of the sinusoids.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 291-295.*





## BILIARY TRACT AND GALLBLADDER

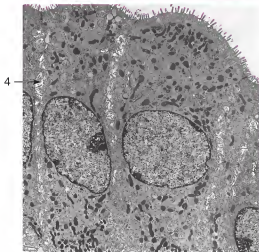
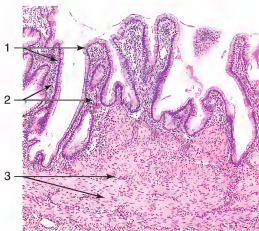
1. Gallbladder
2. Duodenum
3. Hepatopancreatic ampulla
4. Left and right hepatic ducts
5. Common hepatic duct
6. Cystic duct
7. Common bile duct
8. Pancreas
9. Main pancreatic duct

**Key Points:** Bile ductules in the left and right lobes of the liver all come together to form the **left and right hepatic ducts** draining those lobes. These ducts merge to form the **common hepatic duct**, which connects to the **cystic duct** for transport of bile to and from the **gallbladder**. Below the gallbladder, the **common bile duct** carries bile to the **duodenum**. The **main pancreatic duct**, with secretions from the exocrine **pancreas**, joins the common bile duct at the **hepatopancreatic ampulla** just before it enters the wall of the duodenum.

The wall of each of these ducts consists of mucosa with simple cuboidal or columnar epithelium and typical submucosa, muscularis, and serosa. The epithelial cells lining the hepatic, cystic, and common bile ducts resemble those of the liver's bile ductules and are called **cholangiocytes**.

**Clinical Note:** The extrahepatic bile-carrying ducts can all be sites for formation of **adenocarcinomas** or benign **papillomas**, either of which can enlarge sufficiently to obstruct biliary flow. Any such obstruction in the biliary tract can cause bile to back up as far as the bile canaliculi in hepatic lobules, producing leakage of bile into local sinusoids, which results in **jaundice**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 295-297.*



## WALL OF GALLBLADDER

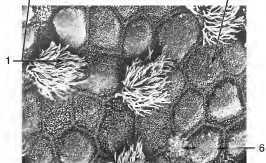
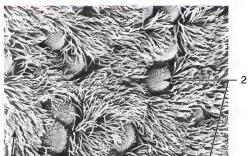
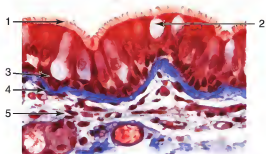
1. Simple epithelium of mucosal folds
2. Lamina propria
3. Muscularis
4. Intercellular spaces along basolateral membranes

**Key Points:** The gallbladder is a hollow, pear-shaped organ attached to the lower surface of the liver, which can store 30 to 50 mL of bile. Its wall has large, irregular **folds of mucosa** with **simple columnar epithelium** and **lamina propria**. The **muscularis** contains variously oriented bundles of smooth muscle fibers that empty the organ upon contraction, which is induced by cholecystokinin (CCK) from the enteroendocrine cells of the duodenum. The outermost layer of the gallbladder wall is a serosa, except where the organ is attached to the liver surface by adventitia.

The lining epithelial cells of the gallbladder, mostly tall cells that have been called **cholecystocytes**, have numerous mitochondria and microvilli and actively absorb water from bile. Large **intercellular spaces** are normally seen ultrastructurally between the basolateral domains of adjacent cells, spaces through which the absorbed water easily flows for uptake by lymphatics and microvasculature in the underlying lamina propria.

**Clinical Note:** Reabsorption of water from bile in the gallbladder can lead to the formation of **gallstones** in the lumen of the gallbladder or biliary ducts, a condition called **cholelithiasis**. This disorder usually originates with bile that already contains excessive amounts of normal bile components. Supersaturation of cholesterol in bile can lead to the formation of **cholesterol stones**, the most common form. Brown or black **pigment stones** can form when bile contains excessive amounts of unconjugated bilirubin, which can result from chronic hemolysis associated with disorders such as sickle cell anemia. Gallstones can lead to biliary obstruction or, more commonly, to inflammation in **acute or chronic cholecystitis**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 295-297.*



## RESPIRATORY EPITHELIUM

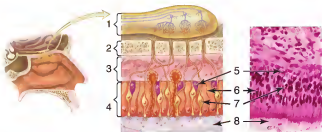
1. Cilia on ciliated columnar cells
2. Mucous (goblet) cells
3. Basal cells
4. Basement membrane
5. Lamina propria
6. Brush cell

**Key Points:** The respiratory epithelium that lines the conducting part of the respiratory tract is the classic ciliated pseudostratified epithelium. It varies somewhat in different areas, but always includes the following:

- The **basement membrane** is robust and appears relatively thick in most areas.
- The most abundant cells are **ciliated columnar cells**, each having 200 to 300 cilia at the apical end. The percentage of such ciliated cells varies in different regions of the respiratory tract.
- Scattered among the ciliated cells and outnumbering them in some areas are **mucous cells**, or **goblet cells**, which secrete a thin layer of mucus that traps inhaled particulate matter and is moved toward the esophagus by the cilia.
- Much less numerous are **brush cells**, each of which has an apical tuft of rigid microvilli. Their function is not clear but they have features of chemoreceptor cells.
- **Basal cells**, which are smaller, rounded, and do not extend to the epithelial surface, include both neuroendocrine **small granule cells** and the **stem cell** population.
- Beneath the basement membrane is a layer of vascularized connective tissue, the **lamina propria**.

**Clinical Note:** Chronic cigarette smoking causes accumulation of toxins in the epithelial cells that immobilize cilia and leads to **squamous metaplasia**, particularly in the bronchi of the lungs, with a change from pseudostratified ciliated columnar to stratified squamous epithelium. Such changes include **cell dysplasia**, which eventually can produce **neoplasia**.

See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 298-300.



## OLFACTORY MUCOSA

1. Olfactory bulb
2. Cribriform plate
3. Lamina propria
4. Olfactory epithelium
5. Basal cells
6. Supporting cells
7. Nuclei of olfactory receptor cells
8. Mucus layer

**Key Points:** The lining in the upper regions of the nasal cavities is **olfactory mucosa** rather than typical respiratory mucosa. This mucosa and the sense of smell involve the following:

- a pseudostratified ciliated columnar epithelium, the **olfactory epithelium**, from which axons of the olfactory receptor cells extend through the **lamina propria** toward the brain;
- the porous **cribriform plate** of the skull's ethmoid bone, with the pores or foramina allowing axon passage into the brain; and
- paired **olfactory bulbs** in the inferior region of the brain.

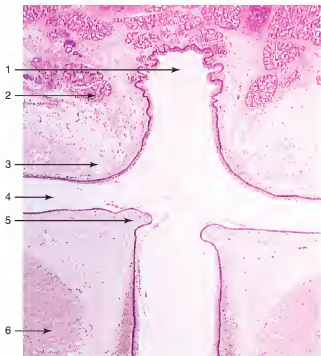
Cells of the olfactory epithelium mediate the sense of smell and include:

- **basal cells** (mainly stem cells) on the basement membrane;
- numerous columnar **supporting cells**, which support the neurons;
- **olfactory receptor cells**, which are bipolar neurons having nuclei located between those of the basal cells and supporting cells; **basal ends** that extend as **axons** through the basement membrane, lamina propria, and the cribriform foramina to synapses in the olfactory bulbs; and **apical ends** that project as bulbous **dendrites** at the epithelial surface, bearing small tufts of long, nonmotile **cilia** transmembrane chemoreceptor proteins for odorant molecules.

The surface of the olfactory epithelium is covered by a **mucus layer** secreted by local olfactory glands, which supports the cilia and the dissolved odorant molecules.

**Clinical Note:** The loss or reduction of the ability to smell, **anosmia** or **hyposmia**, respectively, can be caused by traumatic damage to the ethmoid bone that severs olfactory nerve axons or by damage to the olfactory epithelium caused by intranasal drug use.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 300-301.*





## LARYNX

1. Vestibule of larynx
2. Seromucous glands
3. Vestibular folds
4. Ventricle
5. Vocal folds or cords
6. Vocalis muscle

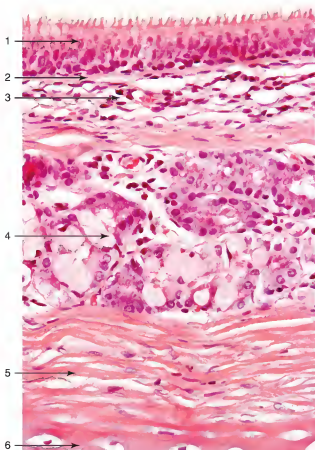
**Key Points:** The **larynx** is the part of the respiratory tract involved with vocalization, located between the pharynx and the trachea. The upper **laryngeal vestibule** is lined by respiratory epithelium, with many small **seromucous glands** in the lamina propria.

At its inferior end, the wall of the vestibule bulges bilaterally as the wide **vestibular folds**, or “false vocal cords,” covered by respiratory epithelium. These folds serve to protect the underlying pair of **vocal folds**, or “true vocal cords,” from which they are separated by a narrow intervening space or **ventricle**.

The **vocal folds** or vocal cords are much thinner than the vestibular folds and project slightly farther into the laryngeal lumen. Unlike the adjacent structures, the vocal folds are covered by stratified squamous epithelium. Beneath this epithelium, these folds contain dense connective tissue with bundles of elastic fibers (the vocal ligament) and a deeper region of striated muscle (the **vocalis muscle**), which moves and changes the tension on the vocal folds and the ligaments, allowing vocalization as air is moved through the larynx.

**Clinical Note:** Inflammation of the larynx, or **laryngitis**, is often due to viral infection and is usually accompanied by **edema** or swelling of the organ’s lamina propria. This changes the shape of the vocal folds or other parts of the larynx, producing **hoarseness** or complete **loss of voice**. **Croup** is a similar syndrome in young children in which edema of the laryngeal mucosa is accompanied by both hoarseness and **coughs** that typically are loud and harsh. Benign reactive polyps, called **singer’s nodules**, can occur in the stratified squamous epithelium of the true vocal cords, also affecting the voice.

*See Mescher AL, Junqueira’s Basic Histology, 12th edition, pages 302-303.*



## WALL OF TRACHEA

1. Pseudostratified ciliated columnar epithelium
2. Basement membrane
3. Lamina propria
4. Seromucous glands
5. Perichondrium of cartilage
6. Hyaline cartilage

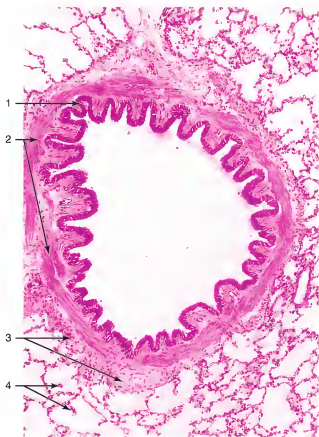
**Key Points:** The trachea is a 12- to 14-cm tube extending from the larynx to the primary bronchi of the lungs. The mucosa lining the trachea has the following layers:

- **Pseudostratified ciliated columnar epithelium**
- A thick **basement membrane**
- Connective tissue of the **lamina propria**
- Numerous, small **seromucous glands**

The **submucosa** contains a series of large, C-shaped **tracheal cartilages**, composed of **hyaline cartilage**, that reinforce the wall and ensure that the lumen of the trachea remains open. The posterior side of the trachea, adjacent to the esophagus, lacks submucosal cartilage to facilitate swallowing. This area contains smooth muscle, the **trachealis muscle**, bridging the ends of the cartilage. Contraction of the trachealis muscle occurs during coughing to narrow the lumen and cause more rapid expulsion of air to help dislodge material blocking the passageway or irritating the tracheal mucosa. The outer layer of the tracheal wall is an **adventitia**.

**Clinical Note:** **Coughing** is a reflex action produced most often by viral infection or other irritation of the trachea or other region of the respiratory tract. A persistent **dry cough**, in which no mucus (phlegm) is produced, can be treated by **cough suppressants** that act on the brain stem and vagus nerve, whereas **productive coughs** are often treated with **expectorants**, which help loosen mucus covering the respiratory mucosa.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 303.*



## BRONCHIOLE

1. Pseudostratified ciliated columnar epithelium
2. Smooth muscle
3. Connective tissue
4. Respiratory alveoli

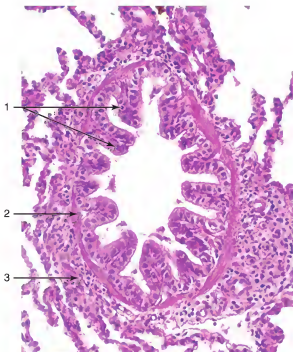
**Key Points:** After the primary bronchi enter the lungs, they branch repeatedly as secondary and tertiary bronchi, which resemble the trachea histologically except that the hyaline cartilage is present as complete rings in the largest bronchial branches and as irregular pieces in the smaller branches. As the cartilage is reduced, the smooth muscle becomes more prominent in the bronchial wall. With additional branching, the cartilage is lost completely, and the smaller (<5 mm) airways are termed **bronchioles**.

Larger bronchioles always have the following features:

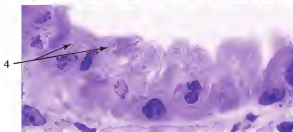
- a lining of **pseudostratified ciliated columnar epithelium** with numerous small folds
- surrounded by a band of smooth muscle, and
- a sparse, variable layer of **connective tissue**.
- The wall of bronchioles is typically surrounded by **respiratory alveoli** of adjacent lung tissue.

**Clinical Note:** Bronchioles constitute the air passages affected most often, especially in young children, by the **measles virus** or **adenovirus**, both of which can cause **bronchiolitis**. If persistent, the inflammation produced by either infection can lead to **obliterative bronchiolitis**, complete or partial closure of the airway lumen due to fibrosis in the wall. Most types of **lung cancer** are **carcinomas** involving epithelial cells lining the larger segments of bronchi, not bronchioles.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 304-307.*



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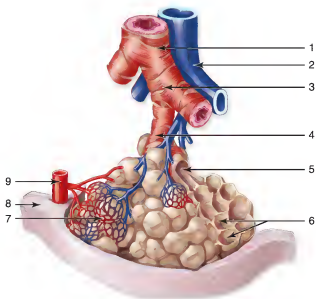
## TERMINAL BRONCHIOLE

1. Epithelium of ciliated cells and Clara cells
2. Smooth muscle
3. Connective tissue
4. Clara cells with apical granules

**Key Points:** **Terminal bronchioles**, the final branches of the airway before gas exchange can occur, are lined by a simple **epithelium of ciliated cells** and **Clara cells**, also known as exocrine bronchiolar cells. Clara cells are typically columnar with **apical granules** for secretion of various proteins, notably components of surfactant. Containing considerable smooth endoplasmic reticulum, these cells also serve to detoxify potentially harmful substances in the inhaled air. The ciliated cells are scattered and more cuboidal. Beneath the epithelium is a layer of **connective tissue** with many elastic fibers surrounding a thin circumferential layer of **smooth muscle**.

**Clinical Note:** Clara cells can give rise to new cells for **bronchiolar epithelial repair** after injury. Besides a role in xenobiotic metabolism, protective roles of Clara cells also include modulating the **innate immune defenses** and the activity of cells involved in local **inflammation**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 305-308.*





## PULMONARY ACINUS

1. Bronchiole
2. Branch of pulmonary artery
3. Terminal bronchiole
4. Respiratory bronchiole
5. Alveolar duct
6. Alveoli
7. Capillary bed around alveoli
8. Connective tissue
9. Branch of pulmonary vein

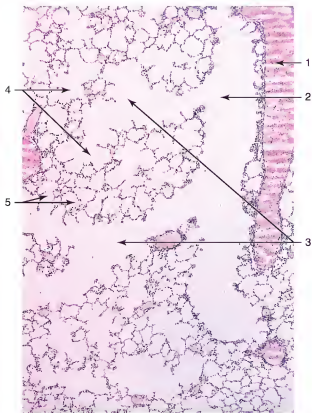
**Key Points:** Each **terminal bronchiole** leads to a larger structure called the **pulmonary lobule**, which is surrounded by a thin layer of **connective tissue** containing microvasculature between the smallest **branches of the pulmonary artery and vein**. Within each lobule are smaller units called **pulmonary acini**, each with the following series of structures carrying air:

- an initial **terminal bronchiole** that branches into
- two or three **respiratory bronchioles**, each leading directly into
- an **alveolar duct**
- that ends in two or three **alveolar sacs**, which are groups of interconnected **alveoli**.

Alveoli are the sites of gaseous exchange between the air and blood in the **capillary beds** within the delicate connective tissue around each alveolus. Collectively, the 400 million alveoli in an adult pair of lungs have a total surface of 75 m<sup>2</sup> for gas exchange.

**Clinical Note:** Obstruction of the air supply in bronchi due to excess mucus or to aspirated material can lead to collapse of pulmonary lobules as blood absorbs gases from the affected alveoli. This condition, called **atelectasis**, is normally reversible when the blockage is relieved, but if the blockage is persistent, it can cause fibrosis and loss of respiratory function.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 305-309.*



## RESPIRATORY BRONCHIOLES, ALVEOLAR DUCTS, AND ALVEOLI

1. Blood vessel
2. Respiratory bronchiole
3. Alveolar ducts
4. Alveolar sacs
5. Alveoli

**Key Points:** The air-filled spaces of the pulmonary acini give a section of lung tissue a typical spongy appearance. Adjacent to very small **branches of the pulmonary artery and vein**, components of each acinus have the following features:

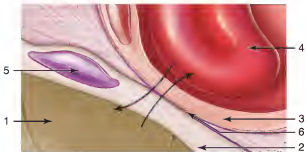
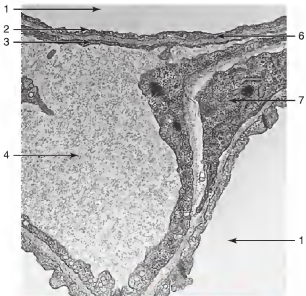
- Each **respiratory bronchiole** has a mucosa similar to that of the terminal bronchiole, with a simple epithelium of Clara cells and cuboidal ciliated cells and a thin surrounding layer of smooth muscle and elastic connective tissue, but the epithelium is interrupted by several bulging respiratory **alveoli** lined by very thin squamous cells.
- Extending from each respiratory bronchiole, the **alveolar duct** wall consists almost exclusively of alveoli and is covered by little connective tissue and smooth muscle.
- Alveolar ducts end in structures called **alveolar sacs**, which are groups of interconnected **alveoli**, where respiratory exchange occurs between air and blood.

Wherever it is located within such a pulmonary acinus, each **alveolus**:

- consists of very thin type I alveolar cells, through which gas exchange occurs;
- contains at least one or two rounded type II alveolar cells, resembling Clara cells; and
- is surrounded by a thin layer of connective tissue containing a capillary bed.

**Clinical Note:** **Emphysema**, a chronic lung disease most commonly caused by cigarette smoking, involves dilation and permanent enlargement of bronchioles and loss of cells in the alveoli and other parts of the pulmonary acini, leading to an irreversible loss of respiratory function. Any type of infection in the respiratory regions of the lung produces the local inflammatory condition called **pneumonia**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 305-310.*



## BLOOD-AIR BARRIER OF ALVEOLI

1. Lumen of alveolus (air)
2. Type I alveolar cell
3. Endothelial cell of capillary
4. Lumen of capillary (blood)
5. Nucleus of type I alveolar cell
6. Fused basement membranes of type I alveolar and endothelial cells
7. Fibroblast in connective tissue of interalveolar septum

**Key Points:** Detailed examination of a respiratory alveolus by transmission electron microscopy shows the following features of the **blood-air barrier**:

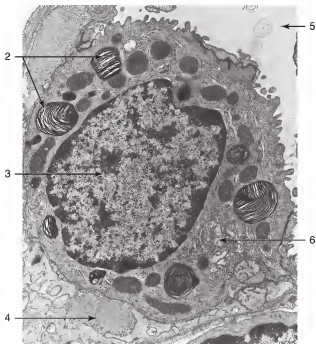
- The **type I alveolar cells**, also called type I pneumocytes, appear mainly as an extremely thin layer of membrane-enclosed cytoplasm making up most of the alveolus and contacting **air in the alveolar lumen**.
- **Endothelial cells**, surrounding the **blood-filled lumen of capillaries**, are also very thin and have broad areas of contact with the type I alveolar cells.
- Basal laminae of these two squamous cells form a single **fused basement membrane** separating the cells at the sites of optimal gas exchange between the air and blood.

The barrier separating air from blood is very thin, varying in thickness from 25 to 50 nm, and provides rapid exchange of dissolved  $O_2$  and  $CO_2$ . Thicker areas of the alveolar wall contain cell nuclei, more extracellular material and occasional **fibroblasts** of connective tissue in interalveolar septa between adjacent alveoli. Motile **alveolar macrophages**, or dust cells, occur in both the alveoli and the interalveolar septa.

**Clinical Note:** Diffuse alveolar damage or adult respiratory distress syndrome can be produced by various types of injuries to the alveolar epithelial and capillary endothelial cells. Common causes of such damage include viral and bacterial **respiratory tract infections**; inhalation of **toxic gases**, chemicals, or air with **excessive oxygen**; and **fat embolism syndrome**, in which adipocytes enter the blood during surgery, circulate, and later block the capillary beds. With removal of the initiating factors, normal alveolar wall components can often be restored with at least partial recovery of function.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 306-312.*

1. What is this cell?



## TYPE II ALVEOLAR CELL

1. Type II alveolar cell
2. Lamellar bodies
3. Nucleus
4. Reticulin fibers
5. Lumen of alveolus
6. Golgi apparatus

**Key Points:** **Type II alveolar cells** (type II pneumocytes) are approximately as numerous in alveoli as type I cells but are rounded and line only about 5% of the **alveolar lumen**. The major function of these cells is secretion of surfactant into the alveolus, producing an aqueous film of phospholipids and proteins lining the type I alveolar cells, a film with low surface tension. Reduced surface tension in the alveolar fluid helps prevent alveolar collapse upon expiration of air and facilitates alveolar inflation during inspiration.

Ultrastructurally, a type II alveolar cell is characterized by:

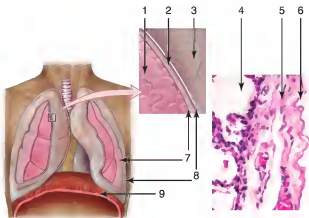
- a large, central, euchromatic **nucleus**;
- rough endoplasmic reticulum and at least one well-developed **Golgi apparatus**, producing some surfactant components; and
- many unusual organelles called **lamellar bodies** with many parallel lamellae composed of the phospholipids and proteins that are secreted from the apical ends of the cells as surfactant.

Type II cells are bound by junctional complexes to adjacent type I cells, and the small amount of connective tissue at their basal ends consists largely of elastic and **reticulin fibers**.

**Clinical Note:** **Infant respiratory distress syndrome**, the leading cause of death in premature babies, is due to incomplete differentiation of type II alveolar cells and a resulting deficit of surfactant and difficulty in expanding the alveoli in breathing. Treatment involves insertion of an endotracheal tube to provide both **continuous positive airway pressure (CPAP)** and **exogenous surfactant**, either synthesized chemically or purified from bovine lungs.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 308-313.*

(Image used with permission from Dr. Mary C. Williams, Pulmonary Center and Department of Anatomy, Boston University School of Medicine.)





## PLEURA

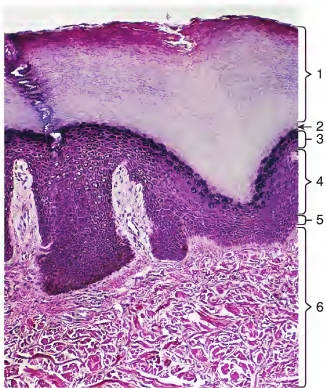
1. Pulmonary lobules
2. Pleural cavity
3. Thoracic wall
4. Alveolus
5. Vascularized connective tissue of visceral pleura
6. Mesothelium (simple squamous) of visceral pleura
7. Visceral pleura
8. Parietal pleura
9. Diaphragm

**Key Points:** The pleura are serous membranes covering the peripheral **pulmonary lobules** of each lung and lining the **thoracic wall**. Pleura are composed of thin sheets of **connective tissue** covered by simple squamous epithelium called **mesothelium**.

The **visceral pleura** cover the lungs, and the **parietal pleura** line the thoracic cavity, which is immediately above the muscular **diaphragm**, which helps provide respiratory movements for expansion of the thoracic cavity and inspiration of air into the lungs. Between the visceral and parietal pleura is a thin space called the **pleural cavity** in which a lubricant fluid secreted by the serous cells prevents friction and adhesion between the apposed layers.

**Clinical Note:** The condition **pneumothorax** is a partially or completely **collapsed lung** caused by air trapped in the pleural cavity, typically resulting from blunt or penetrating trauma to the chest and producing shortness of breath and hypoxia. Inflammation of the pleura, a condition called either **pleuritis** or **pleurisy**, is most commonly caused by an acute viral infection or pneumonia. **Pleural effusion** or fluid build-up in the pleural cavity produces shortness of breath and can be one result of inflamed pleura.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 314-315.*



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## THICK SKIN

1. Stratum corneum
2. Stratum lucidum
3. Stratum granulosum or granular layer
4. Stratum spinosum or spinous layer
5. Stratum basale or basal layer
6. Dermis

**Key Points:** The **thick skin** of the palms and soles consists of epidermal and dermal layers and functions primarily in protection and for the sensation of touch. The **dermis** consists mainly of a thick reticular layer of dense irregular connective tissue with microvasculature. The epidermis consists of specialized cells called **keratinocytes** and is organized in the following five cell layers:

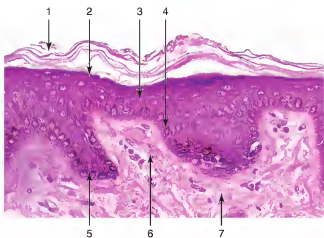
- Bound to the basement membrane with hemidesmosomes is the **basal layer (stratum basale)**, a single layer of cells that includes the stem cells and transit-amplifying cells for keratinocytes. The cells are bound together by numerous desmosomes.
- The **spinous layer**, or **stratum spinosum**, has several layers of polyhedral or flattened keratinocytes with central nuclei, cytoplasm containing newly synthesized keratin bundles (**tonofibrils**), and intercellular desmosomes that may appear as short spines due to cell shrinkage.
- The **granular layer**, or **stratum granulosum**, is composed of progressively flattened, terminally differentiated keratocytes with dense, basophilic **keratohyaline granules** containing **filaggrin** and other proteins forming aggregates with the tonofibrils.
- The **stratum lucidum** is a thin, more translucent layer of keratocytes now lacking nuclei.
- In the very thick superficial **stratum corneum**, the keratocytes form layers of flattened, cornified cells or squames containing dense masses of keratin that protect underlying tissues from friction.

The interface between dermal and epidermal layers is increased by interdigitating epidermal ridges and dermal papillae, as seen here.

**Clinical Note:** **Friction blisters** are lymph-filled spaces created between the epidermis and dermis of thick skin by excessive rubbing, as with ill-fitting shoes or hard use of the hands without gloves. If continued, such conditions produce protective thickening and hardening of the outer epidermal layers, seen as **corns** and **calluses**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 316-320.*

(Image used with permission of Ed Reschke Photography.)



## THIN SKIN

1. Stratum corneum
2. Granular layer or stratum granulosum
3. Spinous layer or stratum spinosum
4. Basal layer or stratum basale
5. Epidermal peg
6. Dermal papilla
7. Dermis

**Key Points:** Most of the body is covered with **thin skin** having **dermis** and an **epidermis** with a **basal layer**, **spinous layer**, **granular layer**, and thin squames of a **stratum corneum** undergoing superficial desquamation. A stratum lucidum is typically not seen.

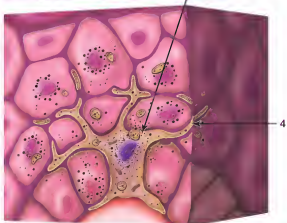
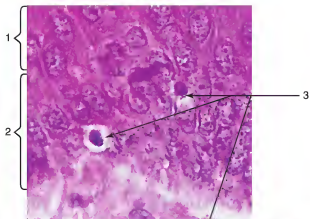
The epidermis of thin skin also contains at least four types of cells that immigrate among the keratinocytes during development:

- **melanocytes**, which are embryonic neural crest derivatives that produce pigmentation of the keratinocytes;
- **dendritic (or Langerhans) cells**, which are antigen-presenting cells important for protection against microorganisms invading the skin;
- **intraepithelial lymphocytes**, usually T cells, which are less numerous than dendritic cells but also important for cutaneous defense; and
- **epithelial tactile (or Merkel) cells**, also derived from the neural crest, which are mechanoreceptors within the basal layer.

In thin skin, the epidermis and dermis interface firmly by means of interdigitating **epidermal pegs** and **dermal papillae**.

**Clinical Note:** In the chronic skin condition **psoriasis**, keratinocytes are produced and differentiate at accelerated rates, causing at least slight thickening of the epidermal layers and increased keratinization and desquamation. Psoriasis is caused by overactive T lymphocyte autoimmune reactions in the skin, which typically also lead to inflammation with redness, irritation, itching, and scaling.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 316-323.*



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## MELANOCYTES

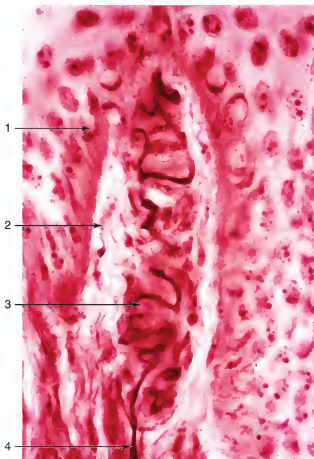
1. Spinous layer or stratum spinosum
2. Basal layer or stratum basale
3. Melanocytes
4. Dendritic processes of melanocyte

**Key Points:** Derived from the embryonic neural crest, **melanocytes** are normally located among the keratinocytes of the **basal layer** in thin skin only and have numerous, long cytoplasmic **dendritic processes** extending among the keratinocytes of the basal and **spinous layers**. Within melanocytes, Golgi-derived vesicles contain **tyrosinase** and other enzymes that synthesize **melanin**, a brown polymer condensed within **melanosomes**. Mature melanosomes are transported along microtubules to the tip of the dendritic processes, where they are transferred from the melanocytes directly into the five or six keratinocytes with which they have contact. Melanin granules accumulate in keratinocytes particularly in the cytoplasmic areas above the nuclei where the ultraviolet-absorbing properties of the pigment help protect DNA from radiation damage.

Skin of different body regions contains different densities of melanocytes, but their average density (roughly 1000 per mm<sup>2</sup> of skin) is similar in all individuals. However, the rates of melanin synthesis and of melanin granule transfer to keratinocytes are increased in people with ancestors from equatorial regions, producing epidermis with varying degrees of color.

**Clinical Note:** **Albinism** is a congenital disorder producing skin **hypopigmentation** due to a defect in tyrosinase or another component of the melanin-producing pathway. An acquired condition called **vitiligo** involves **depigmentation**, often only in affected patches of skin, due to the loss or decreased activity of melanocytes. The causes of melanocyte loss are not clear but may include environmental, genetic, or autoimmune conditions. Melanocytes can normally proliferate in skin to produce **moles**, or **benign melanocytic nevi**, of various types. Changes in the size or appearance of moles are sometimes indicative of dysplasia that can progress further to **malignant melanoma**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 319-322.*





## TACTILE (MEISSNER'S) CORPUSCLE

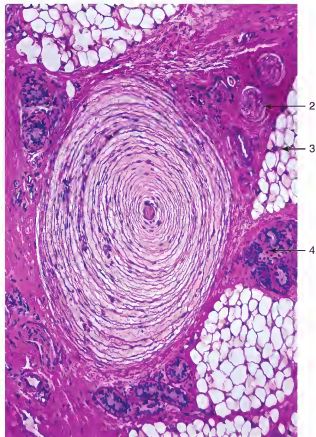
1. Stratum basale of epidermis
2. Dermal papilla
3. Tactile corpuscle
4. Axon

**Key Points:** Tactile (Meissner's) corpuscles are elliptical structures approximately 150  $\mu\text{m}$  long oriented perpendicular to the epidermal surface in many **dermal papillae** just beneath the **stratum basale**. They serve as mechanoreceptors for light touch and are particularly abundant in the skin of the lips and fingers. Each tactile corpuscle contains one or two **unmyelinated sensory axons** extending in a spiral manner around stacked inner layers of modified Schwann cells within a partial or complete capsule of delicate connective tissue. Slight deformations of the tactile corpuscles generate afferent nerve impulses within the axons. Similar sensations are produced in unencapsulated axons associated with the epithelial tactile cells of the epidermal basal layer, in the plexus of axons associated with the deep ends of hair follicles, and in the free nerve endings of axons within epidermis. All of these mediate the sense of light touch, with the free nerve endings also detecting temperature extremes and pain.

**Clinical Note:** The density of tactile corpuscles in skin can be determined approximately by **two-point discrimination tests**. Such neurologic measurements indicate that the number of tactile corpuscles in skin normally declines during adult life. Loss of tactile corpuscles or reduction in their activity can also be detected in **scleroderma** and certain other connective tissue disorders that lead to **sclerosis** (hardening) of the dermis and tightening of the skin.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 324-325.*

1. What is this structure?



18

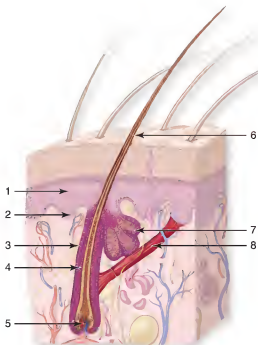
## LAMELLATED (PACINIAN) CORPUSCLE

1. Lamellated corpuscle
2. Nerve
3. Adipose tissue
4. Sweat gland

**Key Points:** Lamellated (or Pacinian) corpuscles are less numerous and much larger than tactile corpuscles. They are oval in shape, up to 1 mm in length, and in skin are located deep in the connective tissue of the dermis or **adipose tissue** of the hypodermis. Like tactile corpuscles, they have a delicate capsule and **unmyelinated axons** from small **nerves** that enter at one end and wind among the multiple **concentric lamellae** formed by flattened cells resembling Schwann cells. Lamellated corpuscles are specialized as mechanoreceptors detecting vibrations and pressure (sustained touch).

**Clinical Note:** Maintenance of the structural integrity of both tactile and lamellated sensory corpuscles is dependent on the nerve supply entering the capsules, with **denervation** or damage to the axons producing degenerative changes in addition to loss of function.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 324-325.*



## PILOSEBACEOUS UNIT

1. Spinous layer or stratum spinosum
2. Basal layer or stratum basale
3. External root sheath
4. Internal root sheath
5. Dermal papilla
6. Hair shaft
7. Sebaceous gland
8. Arrector pili muscle

**Key Points:** The following components associated with the hair follicles of thin skin are often referred to collectively as the “**pilosebaceous unit**”:

- all parts of the **hair follicle**, including the **hair shaft**, the **dermal papilla** at the base of the hair follicle, the **internal root sheath** surrounding the root of the hair, and the external root sheath, which is continuous with the **basal and spinous layers** of the adjacent epidermis;
- the **sebaceous glands**, in which short ducts open into the thin space between the hair shaft and the internal root sheath; and
- the **arrector pili muscle**, a short bundle of smooth muscle fibers anchored within the superficial dermis and attached to the external root sheath, which pulls the hair shaft erect upon contraction.

The oily sebum produced by the sebaceous glands serves to protect the hair shafts and epidermis from dehydration. In animals, raising the hair shafts by contraction of arrector pili muscles helps maintain a layer of warm air near the body surface or serves as a warning signal; in humans, these muscles only produce “goose pimples.” Pilosebaceous units are not present in thick skin, which is hairless.

**Clinical Note:** *Acne vulgaris* is an inflammatory disorder of the pilosebaceous unit that can be expected to occur during adolescence. It involves excessive keratinization within the unit and excess sebum production, both of which contribute to the blockage of ducts in the follicle. Anaerobic bacteria, typically *Propionibacterium acnes*, grow in the accumulated sebum, leading to localized inflammation and neutrophil infiltration. The enlarged follicle that results is called a **comedone**.

See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 325-330.



## HAIR FOLLICLE

1. External root sheath
2. Internal root sheath
3. Connective tissue
4. Cortex
5. Medulla
6. Matrix of the hair bulb
7. Dermal papilla

**Key Points:** The most important parts of a hair follicle are the following:

- The thick **external root sheath** is composed of keratinocyte layers continuous with the deepest layers of the epidermis. It separates the hair follicle from the surrounding **connective tissue** via a thick basement membrane and does not participate in hair formation.
- The thinner **internal root sheath** lines the external sheath from the base of the follicle to the point where the ducts of sebaceous glands enter the follicle.
- At the base of a follicle is the bulging **hair bulb** containing a **matrix** of keratinocytes that have proliferated there, have taken up melanin from local melanocytes, and are undergoing a keratinization process that forms the hair root.
- Keratinocytes of the hair bulb receive nutrients and  $O_2$  from a capillary network within a small **dermal papilla** that is inserted into the base of the bulb.
- Differentiating keratinocytes above the hair matrix constitute a shaft of **hair**, which initially may show three concentric regions:
  - a central, vacuolated **medulla**, only seen in thick hairs;
  - a **cortex** of denser keratin around the medulla or forming the center of thin hairs; and
  - a thin outer **cuticle** of squamous, heavily keratinized cells.

**Clinical Note:** Loss of hair to produce **haldness** or **alopecia** results from a complex combination of genetic and hormonal factors that is not well understood. Arresting mitotic activity in the hair matrix during cancer **chemotherapy** disrupts both the function and the structural integrity of hair follicles and usually leads to rapid, reversible alopecia.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 325-329.*

1. What is this structure?





## SEBACEOUS GLAND

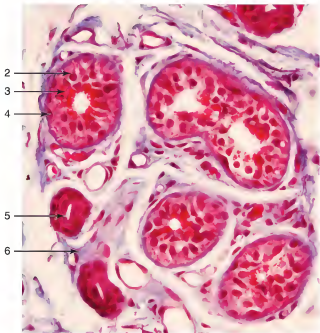
1. Sebaceous gland
2. Hair
3. External root sheath
4. Excretory duct of sebaceous gland
5. Connective tissue capsule
6. Terminally differentiated sebocytes

**Key Points:** Each hair follicle is associated with two or more **sebaceous glands** (with many more in the skin of the face and scalp), all continuous with the lining of the external root sheath and epidermis. Sebaceous glands are branched acinar glands surrounded by dense **connective tissue capsules**. Near the capsule each acinus contains basal cells, which undergo mitosis, move centrally, and undergo terminal differentiation as large, lipid-producing cells called **sebocytes**. Near the lumen, sebocytes become vacuolated, degenerating cells which undergo holocrine secretion to produce the oily mixture called **sebum**. Short **excretory ducts** of the sebaceous acini are continuous with the follicle's **external root sheath** and lead directly to the space surrounding the **hair**.

**Clinical Note:** Sebaceous gland carcinoma is an aggressive but rare form of skin cancer that involves the sebocytes and occurs usually around puberty. Most skin cancers stem from keratinocytes of the epidermis and occur either as **basal cell carcinomas** or **squamous cell carcinomas**, with neither type showing rapid metastasis.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 329-330.*

1. What is shown here?



18

## ECCRINE SWEAT GLAND

1. Eccrine sweat gland
2. Clear secretory cells
3. Dark secretory cells
4. Myoepithelial cells
5. Duct
6. Connective tissue

**Key Points:** Eccrine sweat glands are present in both thin and thick skin over all body regions, with ducts opening to the epidermal surface and producing highly dilute sweat that cools the body by evaporation. These are **simple, coiled tubular glands** with secretory cells active in **merocrine secretion**. The secretory portions of such glands are located deep within the dermis and show a stratified cuboidal epithelium containing three cell types:

- **columnar clear cells**, which rest on the basement membrane and are capable of rapid water transport from the surrounding interstitial space into the glandular lumen;
- **dark cells**, which are near the lumen with their apical ends filled with eosinophilic granules containing various antibacterial peptides released into the water by exocytosis; and
- **myoepithelial cells**, which contract to help force the secretion into the duct.

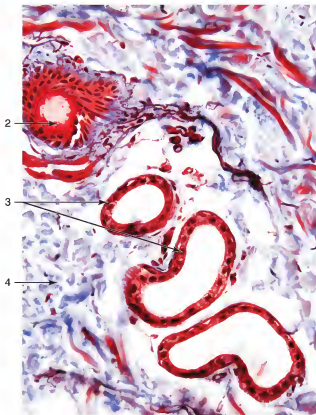
The secretory portions of eccrine sweat glands are closely associated with both capillaries and a plexus of sympathetic nerves.

The coiled secretory portion of the gland leads to a coiled **duct** of smaller diameter composed of stratified cuboidal epithelium. Cells of the duct are neither myoepithelial nor secretory, but function to recover  $\text{Na}^+$  ions from the secreted fluid. The duct passes through dermal **connective tissue** and leads to a channel organized among the keratinocytes of the epidermis.

**Clinical Note:** The sweat of infants with **cystic fibrosis (CF)** is often salty and this is sometimes indicative of this genetic disease. CF patients have defects in a transmembrane conductance regulator (CFTR) of epithelial cells that lead to disruptive accumulations of thick mucus in the respiratory and digestive tracts. Failure to remove salt from sweat is related to the same genetic defect.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 330-331.*

1. What is shown here?



## APOCRINE SWEAT GLAND

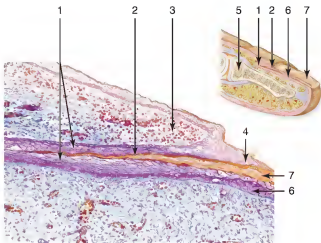
1. Apocrine sweat gland
2. Hair follicle (cross-section)
3. Secretory portion of gland
4. Connective tissue

**Key Points:** Apocrine sweat glands are found only in skin of the axillary, pubic, and breast areolar regions. They develop under the influence of the sex hormones at puberty in association with hair follicles and sebaceous glands in these areas. Other differences from eccrine sweat glands include the following:

- The lumen of the secretory part is much larger, for temporary storage of the secretion.
- The **secretory portion** is of simple cuboidal epithelium with myoepithelial cells surrounding secretory cells with apical granules (also having merocrine, not apocrine, secretion despite what these glands are called).
- Apocrine sweat glands are typically located deeper in the dermis, near the hypodermis.
- Their secretion contains a complex mixture of proteins, lipids, and various organic compounds and differs somewhat in different body regions.
- The sweat acts as a source of pheromones that can subtly influence various sexual and reproductive behaviors.
- Like ducts of eccrine sweat glands, the ducts of apocrine sweat glands are also composed of stratified cuboidal cells, but do not further modify the sweat and typically empty into the **hair follicles** with which they are associated.

**Clinical Note:** Tumors of the pilosebaceous units or sweat glands, collectively called **adnexal tumors**, are usually benign and more commonly involve eccrine rather than apocrine sweat glands. One exception are **hidradenomas**, benign growths that usually occur on skin of the vulva and involve secretory and myoepithelial cells of an apocrine sweat gland.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 330-331.*



## NAIL

1. Nail matrix
2. Nail root
3. Proximal nail fold
4. Eponychium
5. Bone of terminal phalanx
6. Nail bed
7. Nail plate

**Key Points:** Nails on the distal ends of fingers and toes are **plates of keratin** that form in a process analogous to that in hair follicles: keratinocyte proliferation in a deep region called the **nail matrix** followed by differentiation in the **nail root**. The major structures associated with nails include the following:

- The **nail bed** lies beneath the nail plate and is continuous with the basal and squamous layers of the underlying epidermis.
- The proximal region of the nail bed, the **nail matrix**, consists of keratinocytes that proliferate and begin keratinization with a hard form of keratin that does not undergo desquamation.
- Differentiation of these cells in the matrix produces the thick, opaque, partially keratinized **nail root**, which extends distally as the mature and more transparent **nail plate**.
- Cell proliferation in the nail matrix causes growth of the nail as the nail plate is pushed distally.
- The nail plate is bound to the nail bed, with the distal area of attachment called the **hyponychium**, and is surrounded by the lateral nail folds and the **proximal nail fold**.
- The proximal nail fold extends its epidermal component, the **eponychium** or cuticle, over the nail root.

**Clinical Note:** Tight footwear or improper cutting can cause nails to grow into the nail bed (**ingrown nail** or **onychocryptosis**), which can lead to pain and inflammation. The tissues around nails are also subject to various **bacterial or fungal infections**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 328-329.*





## KIDNEY

1. Renal cortex
2. Renal medulla
3. Renal lobe
4. Renal column
5. Major calyx
6. Minor calyx
7. Renal pelvis
8. Renal artery and vein
9. Ureter

**Key Points:** The **ureter** and the **renal artery and vein** all enter the kidney at the concave medial area called the **hilum**. Here the **ureter** expands as the **renal pelvis** and subdivides into two or three **major calyces**, and each of these subdivides further into three or four **minor calyces**. The area around all of these epithelial structures is called the renal sinus and also contains abundant adipose tissue.

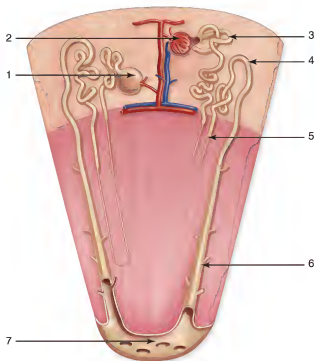
The widest region of the kidney surrounding this sinus and the branching calyces is the **renal medulla**, which contains 8 to 12 structures called the **renal pyramids**. Each of these is a conical structure with its apex, the **renal papilla**, associated with one minor calyx.

Just beneath the kidney's connective tissue **capsule**, the **renal cortex** forms a continuous layer around the organ, completely surrounding the medulla. Extensions of the renal cortex also enter the medulla between the pyramids, forming the **renal columns** where the largest branches of the vasculature are located.

Each pyramid with its associated renal cortex and minor calyx makes up what is referred to as a **renal lobe**.

**Clinical Note:** **Acute renal injury** (or **acute renal failure**) refers to a rapid loss of function throughout the organ and may be due to many different causes. Factors that can precipitate renal failure are classified as "prerenal" if they impact blood flow to functional units in the kidney; "intrarenal" if they involve direct damage to kidney tissues from inflammation, injury, or other causes; and "postrenal" if they result from damage due to blocked urine outflow.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 332-333.*



## RENAL LOBE AND NEPHRONS

1. Renal corpuscle
2. Glomerulus
3. Proximal convoluted tubule
4. Distal convoluted tubule
5. Nephron loop (of Henle)
6. Collecting duct (of Bellini)
7. Renal papilla

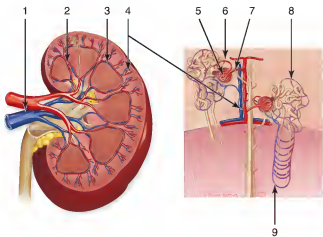
**Key Points:** The cortex and medulla of each renal lobe together contain a hundred thousand functional units of the kidney called **nephrons**. Each nephron begins at a dilated spherical structure in the cortex called a **renal corpuscle**, where blood in a small mass of **capillaries**—the **glomerulus**—is first processed to remove wastes. Each corpuscle is covered by a simple squamous epithelium continuous with a long tubule that makes up the rest of that nephron.

The initial segment of this tubule, composed of simple cuboidal epithelium, is the **proximal convoluted tubule**, which is long, coiled, and located entirely within the cortex. The next part of the nephron descends from the cortex into the medulla and back again, as the **nephron loop** (or loop of Henle). Most of each U-shaped nephron loop is simple squamous epithelium with a thin diameter, but in the outer medulla, the straight portions at each end of the loop are of simple cuboidal epithelium and are thick. The ascending limb of the nephron loop is continuous with the **distal convoluted tubule**, another coiled region in the cortex. (One specialized portion of this distal tubule, associated with the glomerulus, is not shown in this diagram.)

The terminal end of each nephron is the **collecting tubule**. These join to form larger, straight **collecting ducts** (of Bellini), which extend parallel to the nephron loops, converge at the apex of the renal pyramid, called the **renal papilla**, and deliver urine into the minor calyx.

**Clinical Note:** Tubules in all parts of nephrons, but particularly the proximal convoluted tubules, can be involved in **acute tubular necrosis**, a major cause of **acute renal injury**. Injury to the epithelial cells leading to their death can be due to **ischemia** or to **toxic effects** of chemicals that become concentrated within the tubules.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 332-334.*



## RENAL VASCULATURE

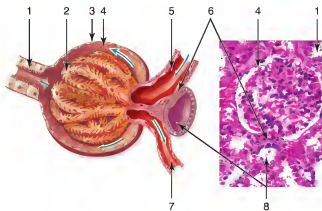
1. Renal artery and vein
2. Interlobar artery and vein
3. Arcuate artery and vein
4. Interlobular artery and vein
5. Glomerulus
6. Efferent arteriole
7. Afferent arteriole
8. Peritubular capillaries
9. Vasa recta

**Key Points:** Understanding the distribution of the renal vasculature is important since the kidneys' main function is to purify the blood. Important vessels and their locations are as follows:

- The **renal arteries** branch to form smaller segments in the renal sinus.
- These extend as the **interlobar arteries** in the renal columns between the medullary renal pyramids.
- These extend as arcs along the junction of the medulla and cortex, extensions called the **arcuate arteries**.
- Branches of these vessels extend into the cortex as the **interlobular arteries**.
- From the interlobular artery, an **afferent arteriole** brings blood to capillaries of each **glomerulus**.
- Glomerular capillaries are emptied by an **efferent arteriole** (not a venule), which carries blood to another set of capillaries, either the **peritubular capillaries** of the cortex or the capillaries of the **vasa recta** associated with the nephron loops.
- Both of these sets of capillaries are drained by the **interlobular veins**, which, like the subsequent converging veins, have the same names as their parallel arteries.

**Clinical Note:** **Sickle cell nephropathy**, one of the most common problems caused by sickle cell disease, occurs when the affected erythrocytes sickle in the vasa recta, due to the low oxygen tension there. The nephropathy results from **renal infarcts**, usually within the renal papillae or pyramids.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 332-336.*



## RENAL CORPUSCLE

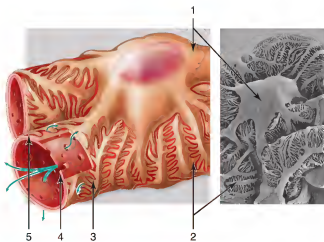
1. Proximal convoluted tubule
2. Podocytes (visceral layer of glomerular capsule)
3. Parietal layer of glomerular capsule
4. Capsular or urinary space
5. Afferent arteriole
6. Juxtaglomerular apparatus
7. Efferent arteriole
8. Distal convoluted tubule

**Key Points:** The **renal corpuscle** of each nephron is spherical, about 200  $\mu\text{m}$  in diameter, and located in the cortex. Each renal corpuscle consists of the following parts:

- A small mass of fenestrated capillaries, the **glomerulus**, is connected at the corpuscle's vascular pole to the **afferent and efferent arterioles**.
- Surrounding the glomerulus is a two-layered **glomerular capsule**, with the outer parietal layer continuous with the **proximal convoluted tubule** at the corpuscle's tubular pole.
- At the vascular pole, the **simple squamous parietal layer** of the capsule is continuous with the inner or **visceral layer of podocytes**, unique epithelial cells that associate intimately with the surfaces of the glomerular capillaries.
- Between the visceral and parietal layers of the corpuscle is the **capsular or urinary space**, which is emptied by the proximal convoluted tubule.
- At the vascular pole next to each renal corpuscle is a **juxtaglomerular apparatus**, which monitors ion concentrations in the tubular fluid and helps regulate blood pressure.

**Clinical Note:** There are many different **glomerular diseases** involving the renal corpuscles, with different causes calling for different treatments. Accurate diagnoses of such disorders by pathologists require sampling of the cortex and may involve examination of the renal corpuscles by immunofluorescence light microscopy or even by transmission electron microscopy.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 333-337.*





## PODOCYTES AND GLOMERULAR CAPILLARIES

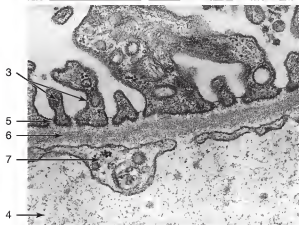
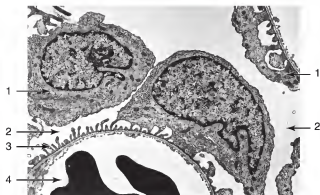
1. Podocyte cell body
2. Pedicel processes
3. Filtration slits
4. Fenestrated endothelial cell of capillary
5. Glomerular basement membrane

**Key Points:** The **podocytes** are unique epithelial cells associated with capillaries of the glomerulus. Each podocyte wraps itself around a portion of capillary with a few large primary processes from which many smaller **secondary processes** or **pedicels** extend and interdigitate to cover most of the capillary surface. Between the pedicels are very narrow spaces called **filtration slits**. The basal lamina of the endothelial cells fuses with basal lamina made by the podocytes to form the **glomerular basement membrane**. With the filtration slits between the surrounding pedicels and the fenestrations of the capillary wall, the filtration membrane is the only structure separating plasma in the capillaries from the filtrate in the corpuscle's urinary space.

Also present among these capillaries and podocytes is a more sparse population of **mesangial cells**, which resemble pericytes. Mesangial cells synthesize extracellular matrix, remove protein complexes clogging the filter, and provide innate immune defense of the glomerulus.

**Clinical Note:** Inflammation within the glomeruli, or **glomerulonephritis**, which can be either acute or chronic, usually stems from humoral immune reactions. Varieties of this condition involve the deposition of circulating antibody-antigen complexes within glomeruli or circulating antibodies binding to either glomerular antigens or extraneous antigens deposited in the glomeruli. Regardless of the source, the accumulating immune complexes can then elicit a local inflammatory response.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 333-339.*



## GLOMERULAR FILTRATION BARRIER

1. Podocyte
2. Urinary space
3. Pedicels
4. Blood in capillary
5. Filtration slit
6. Glomerular basement membrane (GBM)
7. Fenestrated capillary endothelial cell

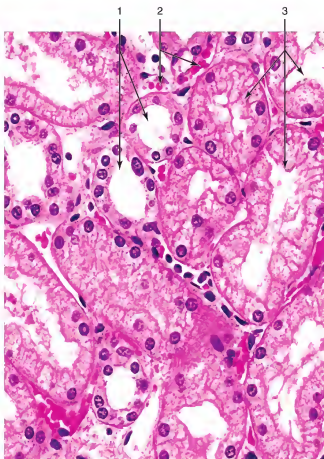
**Key Points:** The glomerular filtration apparatus within each renal corpuscle consists of three components:

- The **fenestrated endothelium of the glomerular capillaries**: These fenestrations are typically 100 to 150 nm in diameter and more abundant than in capillaries elsewhere.
- The **glomerular basement membrane (GBM)**: This thick (250–400 nm) extracellular structure is produced by fusion of the basal laminae of the endothelial cells and the podocytes and maintained by both cells.
- The numerous small **pedicels** extending across the capillary surface from the **podocytes's primary processes**: Aligned in parallel, the pedicels are separated from one another by thin **filtration slits**, which are only about 25 nm wide and are spanned by extremely thin **slit diaphragms**.

With arterioles at each end of the glomerular capillaries, **blood in the capillaries** is under increased hydrostatic pressure, which moves much of the plasma out of the capillaries across the filtration apparatus. The thick GBM prevents movement of plasma proteins greater than 70,000 Da in size (about the size of albumin), but all smaller solutes are moved with the water through the filter into the **urinary space** for drainage into the proximal convoluted tubule. The total area of filter in the glomeruli of all nephrons is estimated at 500 cm<sup>2</sup>, capable of filtering 125 mL of plasma per minute (or the entire blood volume 60 times each day).

**Clinical Note:** **Diabetic glomerulosclerosis**, the thickening and loss of function in the GBM produced as part of the systemic microvascular sclerosis in diabetes mellitus, is the leading cause in the United States of (irreversible) **end-stage kidney disease**. Treatment requires either a **kidney transplant** or regular **artificial hemodialysis**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 333–339.*



## RENAL CORTEX

1. Distal convoluted tubules
2. Peritubular capillaries
3. Proximal convoluted tubules

**Key Points:** The **renal cortex** contains all of the renal corpuscles and most of the proximal and distal convoluted tubular portions of the nephrons. These tubules appear histologically as transverse or oblique sections occupying most of the cortex. Between the convoluted tubules is a sparse connective tissue containing the **peritubular capillaries**.

**Proximal convoluted tubules** contain the filtrate draining from the tubular poles of corpuscles and have the following features:

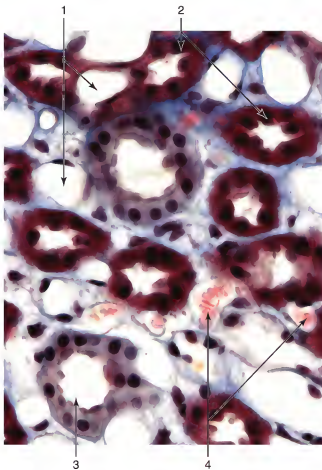
- They are tubes made of large, simple cuboidal epithelial cells with long microvilli. Together with proteins in the filtrate, the microvilli may occupy most of the lumen of these tubules.
- In these long tubules, most water and useful components (e.g., polypeptides, sugars, amino acids) removed from blood in the glomerulus are reabsorbed from the lumen and passed through the cells for return to the blood in the peritubular capillaries.

**Distal convoluted tubules** are less than half as long as the proximal tubules and therefore less numerous in sections. They are characterized by the following:

- They are tubes of simple cuboidal cells, with very few microvilli, and therefore, the lumens have a more open or empty appearance.
- The epithelial cells are smaller than those of proximal tubules, with more prominent nuclei, and typically stain more lightly because of fewer mitochondria and other organelles.
- Cells of the distal tubules absorb  $\text{Na}^+$  ions and secrete  $\text{K}^+$  ions into the luminal fluid under the influence of **aldosterone** from the adrenal glands. Ammonium is also secreted into the filtrate by these cells.

**Clinical Note:** **Polycystic kidney disease** is an inherited disorder in which the normal cortical organization of both kidneys is lost due to the formation of multiple, large, fluid-filled cysts. The cysts may arise from any epithelial cells of the nephron and can lead to gross kidney enlargement and loss of renal function.

See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 333-342.



## RENAL MEDULLA

1. Thin limb of nephron loop
2. Thick limb of nephron loop
3. Collecting duct
4. Capillaries of the vasa recta

**Key Points:** The **renal medulla** is made up largely of the **renal pyramids**, which contain the nephron loops (located between the proximal and distal tubules of each nephron) and the collecting ducts. Surrounding these tubes is an interstitium in which **capillaries of the vasa recta** are located.

The **nephron loops (of Henle)** are important primarily in adjusting ion levels in the filtrate and generally concentrating the urine. They have the following features:

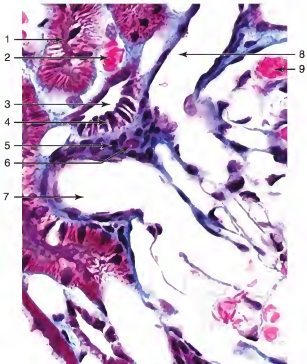
- At the initial and terminal parts of the loop are **thick descending and ascending limbs** (straight portions continuous with the proximal and distal convoluted tubules, respectively) composed of simple cuboidal epithelial cells similar to the convoluted tubules structurally and functionally.
- Between these thick limbs is an intervening thin limb of variable length composed of very thin simple squamous epithelial cells. Water drawn passively from the thin limbs is taken up by capillaries of the vasa recta.

**Collecting ducts** are continuous with the distal tubules via the collecting tubules and are characterized by the following:

- They are composed of simple epithelium in which the cells become more columnar as the ducts approach the renal papilla.
- Membranes of the pale-staining principal cells of these ducts have abundant aquaporin water channels, which allow further recovery of water here under the influence of **antidiuretic hormone** from the posterior pituitary.

**Clinical Note:** Bacterial infections of the urinary tract can lead to inflammation of the renal pelvis and calyces, or **pyelonephritis**. In acute pyelonephritis, bacteria often move from one or more minor calyces into the associated renal papilla, causing accumulation of neutrophils in the collecting ducts.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 333-342.*





## JUXTAGLOMERULAR APPARATUS

1. Proximal convoluted tubule
2. Peritubular capillary
3. Distal convoluted tubule
4. Macula densa
5. Juxtaglomerular cells
6. Lacis cell
7. Afferent arteriole
8. Efferent arteriole
9. Glomerular capillary

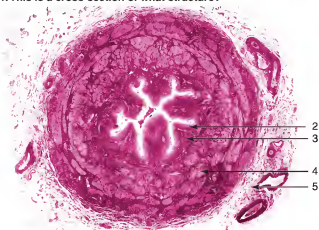
**Key Points:** Next to each glomerulus is a **juxtaglomerular apparatus (JGA)** formed by contact between the distal convoluted tubule and the afferent arteriole. JGAs collectively regulate the glomerular filtration rate and play a major role in regulating blood pressure. Each JGA has the following components:

- A short region of the **afferent arteriole** in which muscle cells of the tunica media are specialized for secretion rather than contraction. These **juxtaglomerular cells** contain granules of the protein **renin**, which upon release into the blood activates the angiotensin-aldosterone system to help regulate hemodynamic properties of the **glomerular capillaries**, the glomerular filtration rate, and sodium homeostasis.
- Associated with these cells is a short region of the distal convoluted tubule in which the epithelial cells have become columnar, forming a thickened structure called the **macula densa**. Cells of this structure both monitor the  $\text{Na}^+$  concentration within the tubule and regulate the secretion of renin into the blood.
- Extraglomerular mesangial cells, called **lacis cells**. Located between the afferent and efferent arterioles, lacis cells may resemble mesangial cells by having contractile or phagocytic properties, but their function is not clear.

**Clinical Note:** **Stenosis** (narrowing) of the renal artery or its major branches, usually due to **intrarenal atherosclerosis**, can change the hemodynamics within the glomerulus, affecting the activity of the JGA, and produce a moderate elevation of systemic blood pressure termed **renovascular hypertension**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 333-342.*

1. This is a cross-section of what structure?



## URETER

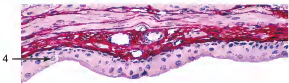
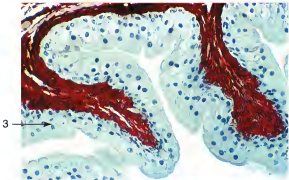
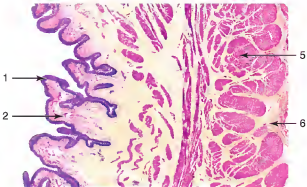
1. Ureter
2. Urothelium or transitional epithelium
3. Lamina propria
4. Muscularis
5. Adventitia

**Key Points:** A **ureter** drains urine from each kidney to the bladder. Like the calyces, the renal pelvis, and the bladder, the ureters are lined by **urothelium or transitional epithelium**, which protects the underlying tissues from the cytotoxic effects of urine. Other histologic highlights of the ureters include the following:

- The mucosa, with both the thick **urothelium** and the **lamina propria**, has longitudinal folds produced by the surrounding muscularis.
- The **muscularis** is thick and prominent, moving urine by peristalsis, with the inner layers of smooth muscle disposed longitudinally and the outer layers circular.
- The muscularis is surrounded by a thick **adventitia**.

**Clinical Note:** A common problem involving the ureters is their obstruction by **renal calculi (kidney stones)**, which are formed in the renal pelvis or calyces, usually from calcium salts (oxalate or phosphate) or uric acid. Although urate stones are usually smooth and small, calcium stones can become large and irritate the mucosa. Most kidney stones are asymptomatic, but besides causing an obstruction that can lead to renal problems, movement of stones from the renal pelvis into the ureter can cause extreme pain on the affected side of the body. Problems caused by such stones can be treated by either surgical removal of the stone or its disintegration using focused ultrasonic shock waves in a procedure called **lithotripsy**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 342-345.*



## URINARY BLADDER WALL

1. Urothelium (transitional epithelium)
2. Lamina propria
3. Urothelium of empty bladder
4. Urothelium of full bladder
5. Muscularis
6. Adventitia

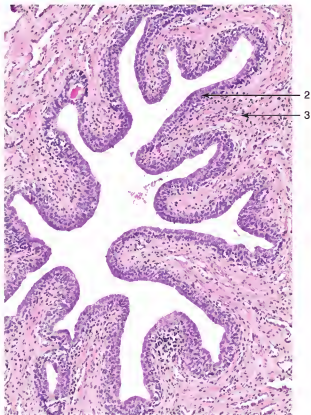
**Key Points:** The **urinary bladder** is an expandable, muscular sac that provides for temporary storage of urine. The main features of its wall include the following:

- The lining of **urothelium or transitional epithelium**, which is best-developed in the bladder, covers a thin, folded **lamina propria** and thin submucosa.
- Superficial cells of the urothelium, called **umbrella cells**, are larger and more bulbous than underlying cells. The apical membrane of umbrella cells contains many protein-rich plaques that protect against the hypertonic and toxic effects of the stored urine. **Emptying the bladder** (micturition) allows folding of the mucosa and folding of the apical membrane plaques, and the urothelium appears thicker due to lateral movements of cells below the umbrella cells.
- Micturition occurs by contraction of the **muscularis**, in which three layers of smooth muscle are interwoven and collectively called the detrusor muscle.
- The outermost layer of the bladder wall is **adventitia** (except for the peritoneum covering its superior surface).

**Clinical Note:** Cystitis, or inflammation of the bladder mucosa, is the most frequent problem involving this organ. Such inflammation is common during urinary tract infections but can also occur as a result of immunodeficiency, urinary catheterization, radiation, or chemotherapy. Chronic cystitis can cause an **unstable urothelium**, with **benign urothelial changes** involving hyperplasia or metaplasia. Bladder cancer is usually some form of **transitional cell carcinoma** arising from unstable urothelium.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 342-346.*

1. This is a cross-section of what structure?



## URETHRA

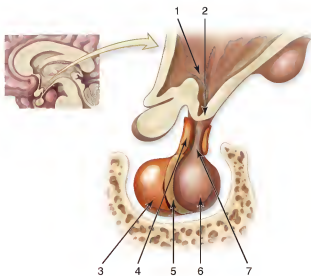
1. Urethra
2. Epithelium of urethral lining
3. Lamina propria

**Key Points:** The tube draining the urinary bladder, the **urethra**, has the following features:

- The mucosa (epithelial lining and **lamina propria**) has prominent longitudinal folds.
- The **epithelium** lining the lumen is urothelium near the bladder but changes to stratified and pseudostratified columnar epithelium in more distal regions.
- In men, the urethra is longer than in women and serves another function: transport of sperm during sexual intercourse. The male urethra has three regions:
  - the 3- to 4-cm **prostatic urethra** lined by urothelium and located within the prostate gland;
  - the 1-cm **membranous urethra** lined by stratified and pseudostratified columnar epithelium and passing through the urogenital diaphragm of the pelvic floor, with skeletal muscles of that diaphragm acting as an **external urethral sphincter**; and
  - the much longer **spongy urethra** also lined by stratified and pseudostratified columnar epithelium and enclosed within the spongy erectile tissue of the penis.
- The muscularis of the urethra is much thinner and less organized than that of the ureter.

**Clinical Note:** Urinary tract infections, usually involving coliform bacteria or *Chlamydia*, often produce **urethritis** and, in women, may also lead to cystitis because of the short urethra. Such infections are usually accompanied by a persistent or more frequent urge to urinate, and urethritis may produce pain or difficulty during urination (**dysuria**).

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 344-347.*





## PITUITARY GLAND

1. Hypothalamus
2. Median eminence
3. Anterior pituitary pars distalis
4. Anterior pituitary pars tuberalis
5. Anterior pituitary pars intermedia
6. Posterior pituitary pars nervosa
7. Posterior pituitary infundibulum

**Key Points:** The **pituitary gland**, or hypophysis, lies below the brain in a depression within the sphenoid bone called the sella turcica. The gland has two major parts, with different embryonic origins and functions.

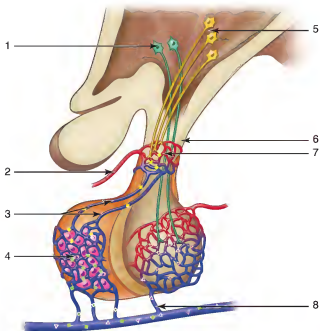
The **posterior pituitary gland**, or neurohypophysis, forms as part of the developing brain to which it remains connected by an **infundibulum** continuous with the **median eminence** of the **hypothalamus**. The lower portion of the infundibulum expands greatly as the **pars nervosa**, which is adjacent to the anterior pituitary.

The **anterior pituitary gland**, or **adenohypophysis**, forms in the early embryo from the hypophysial (Rathke's) pouch, growing and detaching from the roof of the oral cavity. It develops three major regions:

- The large anterior **pars distalis** accounts for 75% of the adenohypophysis.
- The thin **pars tuberalis** is a funnel-shaped region that surrounds the infundibulum of the posterior pituitary gland.
- The thin **pars intermedia** is the area adjacent to the pars nervosa of the posterior pituitary.

**Clinical Note:** **Hypopituitarism** refers to deficient secretion of one or more hormones typically caused by benign **pituitary adenomas** in one part of the gland compressing glandular tissue in adjacent parts, interfering with secretion there.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 348-335.*



## HYPOTHALAMIC-HYPOPHYSIAL TRACTS AND PORTAL SYSTEM

1. Secretory neurons of supraoptic and paraventricular nuclei
2. Superior hypophyseal artery
3. Hypophyseal portal veins
4. Secondary capillary plexus
5. Neurosecretory cells in hypothalamus
6. Infundibulum
7. Primary capillary plexus
8. Hypophyseal vein

**Key Points:** Tracts of axons from specific hypothalamic nuclei to the pituitary gland are of two types, with different functions:

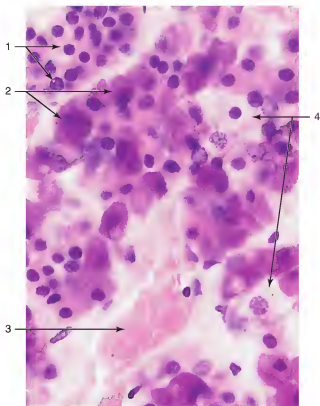
- Axons from neurons of the **supraoptic and paraventricular nuclei** extend along the **infundibulum** to the **posterior pituitary pars nervosa**, where they secrete hormones that are then taken up by a plexus of fenestrated capillaries for bodily distribution.
- **Secretory neurons** of other hypothalamic nuclei extend axons as far as the **infundibulum**, where peptides they release are taken up by the **primary capillary plexus** for transport to the anterior pituitary. There, these hypothalamic peptides act as releasing or inhibiting factors to regulate anterior pituitary hormone secretion.

Blood vessels of the **hypothalamic-hypophyseal portal system** transport the hypothalamic factors to the anterior pituitary and nearby vessels carry the pituitary hormones into the circulation. Important vessels include the following:

- The **superior hypophyseal artery** supplies blood to the **primary capillary plexus**.
- This capillary plexus at the infundibulum leads to small **hypophyseal portal veins**, which connect it to the **secondary capillary plexus** in the pars distalis. These two sets of capillaries and their connecting veins constitute the portal system.
- The **inferior hypophyseal artery** supplies blood to another capillary plexus located in the **posterior pituitary pars nervosa** for uptake of hormones secreted there.
- All the capillary networks drain into **hypophyseal veins** leaving the pituitary gland.

**Clinical Note:** Benign **pituitary adenomas** can occasionally bleed and produce a hemorrhagic infarction termed **pituitary apoplexy**. These usually cause no endocrine problems because adequate tissue is unaffected and remains functional.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 351-352.*



## ANTERIOR PITUITARY PARS DISTALIS

1. Acidophils
2. Basophils
3. Sinusoid
4. Chromophobe cells

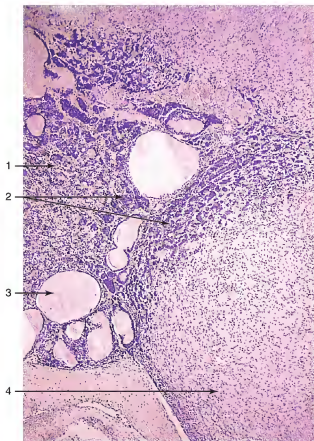
**Key Points:** The **pars distalis** of the anterior pituitary contains a delicate stroma with many **sinusoids** of the secondary capillary plexus. With most routine stains, three types of secretory or parenchymal cells can be recognized, based on the staining of cytoplasmic granules:

- **Acidophils**, which can be subdivided further using immunohistochemistry or transmission electron microscopy (TEM) into:
  - abundant (50% of total) **somatotropic cells**, secreting somatotropin (growth hormone); and
  - less numerous (15%-20%) **lactotropic (mammatropic) cells**, secreting prolactin.
- **Basophils**, which are typically less numerous than acidophils and can be subdivided by immunohistochemistry or TEM as:
  - **corticotropic cells**, secreting adrenocorticotropic hormone (ACTH) and lipotropic hormone (LTH), both derived by cleavage of a larger protein, pro-opiomelanocortin (POMC);
  - **gonadotropic cells**, secreting both follicle-stimulating hormone (FSH) and luteinizing hormone (LH); and
  - **thyrotropic cells**, secreting thyroid-stimulating hormone (TSH).
- **Chromophobe cells**, which are much less numerous, are undifferentiated cells and, lacking most granules, have essentially unstained cytoplasm.

Secretion of these hormones from acidophils and basophils is largely controlled by hypothalamic releasing factors transported to the pars distalis by the portal system. Acidophil secretion is also regulated by hypothalamic factors that inhibit hormone release.

**Clinical Note:** Benign **pituitary adenomas** often produce excessive numbers of functional acidophils or basophils. Adenomas involving somatotropic cells can cause **gigantism** if occurring in children before closure of the long bones' epiphyseal plates or **acromegaly** in adults, with musculoskeletal, neurologic, and other medical consequences.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 351-356.*



## ANTERIOR PITUITARY PARS INTERMEDIA

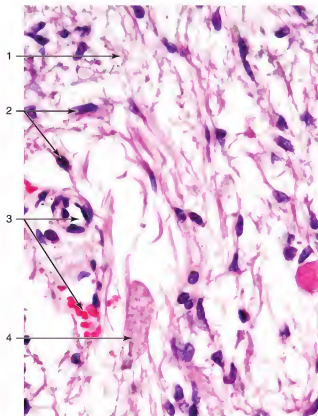
1. Pars distalis
2. Pars intermedia with numerous basophils
3. Colloid-filled cysts
4. Pars nervosa

**Key Points:** The **anterior pituitary pars intermedia** is a narrow zone of tissue located between the **pars distalis** and the less well-stained nervous tissue of the **pars nervosa** in the posterior pituitary. The pars intermedia contains:

- clusters of **basophils** resembling those of the pars distalis, mostly corticotropic cells but of uncertain physiologic significance; and
- a series of characteristic small, **colloid-filled cysts** that represent remnants of the embryonic hypophysial pouch but whose functional significance also remains uncertain.

**Clinical Note:** Pituitary adenomas involving corticotropic cells, which at least in some domestic animals such as horses involve the pars intermedia, can lead to **Cushing disease**, which is characterized by excessive secretion of adrenocorticotrophic hormone (ACTH).

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 351-352 and 357.*





## POSTERIOR PITUITARY PARS NERVOSA

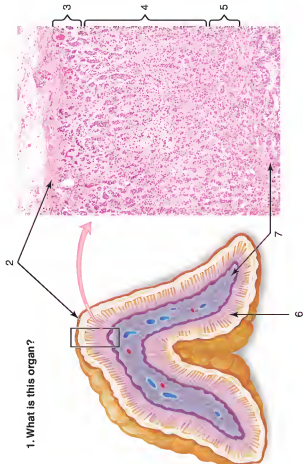
1. Axons from hypothalamus
2. Pituicyte
3. Capillaries
4. Neurosecretory (Herring) body

**Key Points:** As a derivative from the developing brain, the **pituitary gland pars nervosa** is composed of nervous tissue that stains very differently from the epithelial parenchymal cells in all parts of the anterior pituitary. The pars nervosa contains the following important components:

- Unmyelinated **axons** from neuronal cell bodies in the hypothalamic **supraoptic and paraventricular nuclei** secrete the peptide hormones oxytocin and vasopressin (also called antidiuretic hormone [ADH]) in the pars nervosa.
- Both hormones are stored before their release in dilated axonal regions known as **neurosecretory (Herring) bodies**, where they are bound to neurophysins, carrier proteins synthesized with the hormone as a single polypeptide, and then cleaved.
- The numerous cells associated with the axons of the pars nervosa are **pituicytes**, which resemble astrocytes in other central nervous system tissues and provide support for the axons.
- A network of **capillaries** carries away oxytocin and vasopressin released from the neurosecretory bodies.

**Clinical Note:** Posterior pituitary function is adversely affected by heritable mutations in the gene for vasopressin (ADH)-neurophysin, by compression from a **craniopharyngioma** (a tumor that forms from epithelial remnants of Rathke's pouch) or other brain tumors, and by **head trauma** or damage from surgery to remove anterior pituitary adenomas. By lowering levels of vasopressin, such conditions can produce **central diabetes insipidus**, a disorder characterized by inability to concentrate urine, which leads to frequent urination (**polyuria**) and increased thirst (**polydipsia**).

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 353-359.*



## ADRENAL GLAND

1. Adrenal gland
2. Capsule
3. Zona glomerulosa of adrenal cortex
4. Zona fasciculata of adrenal cortex
5. Zona reticularis of adrenal cortex
6. Adrenal cortex
7. Adrenal medulla

**Key Points:** Situated at the superior end of each kidney, the paired **adrenal glands** each weigh about 8 g. Each gland consists of two very different regions: the thick **adrenal cortex** beneath the connective tissue **capsule** and the central **adrenal medulla**.

The **adrenal cortex** can be subdivided into three concentric zones of steroid hormone-secreting epithelial cells, all supported by a well-vascularized stroma:

- Cells of the outermost **zona glomerulosa** form rounded clusters and mainly produce aldosterone, a mineralocorticoid that helps regulate electrolyte homeostasis.
- Cells of the middle layer, the **zona fasciculata**, which comprises about two-thirds of the adrenal cortex, are arranged as long cords and secrete cortisol and other glucocorticoids affecting carbohydrate metabolism.
- Cells of the deepest layer, the **zona reticularis**, form a network of irregular cords and produce primarily the weak androgen dehydroepiandrosterone (DHEA).

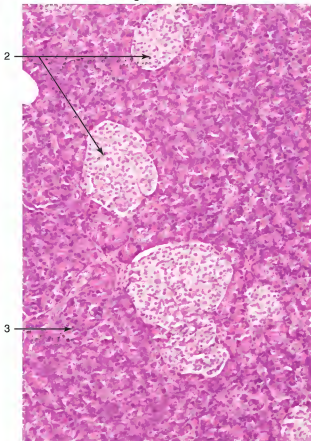
The **adrenal medulla** contains the following:

- a plexus of sinusoids and collecting veins draining both this region and the cortex; and
- a parenchyma of large, pale-staining cells secreting either epinephrine or norepinephrine and usually called chromaffin cells. These catecholamine-producing cells are derived from embryonic neural crest cells.

**Clinical Note:** Addison disease, or **adrenal cortical insufficiency**, is a disorder, usually autoimmune in origin that causes degeneration in any layer of the adrenal cortex, with concomitant loss of glucocorticoid, mineralocorticoid, or androgen production. In the adrenal medulla, benign **pheochromocytomas** periodically secrete high levels of catecholamines that cause swings in blood pressure between hypertension and hypotension.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 354-358 and 361-363.*

1. Tissue from what organ is shown here?



20

## PANCREATIC ISLETS

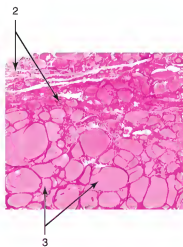
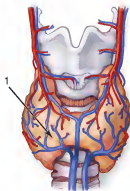
1. Pancreas
2. Pancreatic islets (of Langerhans)
3. Exocrine acinar tissue

**Key Points:** The **pancreatic islets (islets of Langerhans)** are small (100-200  $\mu\text{m}$  in diameter) clusters of densely vascularized endocrine tissue enclosed within fine reticular capsules and embedded in the surrounding pancreatic **exocrine acinar tissue**, comprising 1 to 2% of the organ's volume. Cells of the islets are typically smaller and more pale staining than the acinar cells. Several types of polypeptide hormone-secreting cells can be distinguished in a pancreatic islet, most easily by immunohistochemistry:

- Approximately two-thirds of the cells are centrally located **beta ( $\beta$ ) cells** producing insulin, which promotes glucose uptake by cells, reducing blood sugar levels.
- The second most abundant cells are the peripherally located **alpha ( $\alpha$ ) cells** secreting glucagon, which stimulates glucose release from stored glycogen and lipids, raising blood sugar levels.
- Scattered **delta ( $\delta$ ) cells** secrete the polypeptide somatostatin, which has paracrine effects inhibiting the activity of alpha and beta cells.
- Rare **F (or PP) cells** secrete pancreatic polypeptide, which together with hormones from certain other islet cells supplements the enteroendocrine cells of the digestive system.

**Clinical Note:** **Diabetes mellitus** is characterized by loss of the insulin effect and a subsequent failure of cells to take up glucose, leading to elevated blood sugar or **hyperglycemia**. **Type 1 diabetes**, or **insulin-dependent diabetes mellitus (IDDM)**, is caused by loss of the beta cells from autoimmune destruction and is treated by regular injections of insulin. In **type 2 diabetes**, or **non-insulin-dependent diabetes mellitus (NIDDM)**, beta cells are present but fail to produce adequate levels of insulin in response to hyperglycemia, and the peripheral target cells "resist" or no longer respond to the hormone. Type 2 diabetes commonly occurs with obesity, and poorly understood, multifactorial genetic components are also important in the onset of the disease.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 359 and 364-365.*



## THYROID GLAND

1. Thyroid gland
2. Capsule and septa connective tissue
3. Follicles with colloid containing thyroglobulin

**Key Points:** Located anterior and just inferior to the larynx, the **thyroid gland** consists of two lobes united by an isthmus and completely enclosed by a connective tissue **capsule** penetrated by numerous small arteries and veins. Septa extend from the capsule and subdivide the organ into lobules with well-vascularized stroma. The thyroid parenchyma consists of numerous **follicles** of various sizes, each having a simple cuboidal epithelium and a lumen filled with homogenous, lightly stained **colloid**.

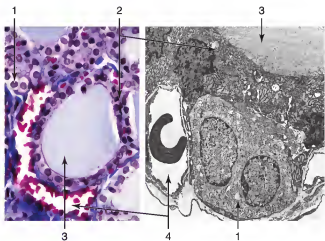
There are two key cells in the thyroid gland:

- The epithelial **follicular cells** that compose the wall of follicles secrete the large glycoprotein thyroglobulin into the lumen, forming most of the colloidal material, and then process the modified (iodinated) protein for the production of active thyroid hormone, which is released into the stroma for uptake by capillaries. The thyroid hormones  $T_3$  and  $T_4$  regulate metabolic activity in cells throughout the body.
- Less numerous **parafollicular cells** (or **C cells**) secrete the polypeptide hormone calcitonin, which helps regulate blood calcium levels by affecting the activity of osteoclasts.

**Clinical Note:** **Graves disease** is an autoimmune disorder in which antibodies against the thyroid-stimulating hormone (TSH) receptor produce chronic stimulation of the follicular cells and release of thyroid hormones (**hyperthyroidism**), which causes a hypermetabolic state marked by weight loss, nervousness, sweating, heat intolerance, and other features.

**Hypothyroidism**, with reduced thyroid hormone levels, can be caused by **thyroiditis** or inadequate secretion of TSH by the anterior pituitary gland and is often manifested by tiredness, weight gain, intolerance of cold, and decreased ability to concentrate.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 360-365 and 367-368.*





## THYROID FOLLICLES

1. Parafollicular or C cells
2. Follicular cells
3. Colloid in follicular lumen
4. Capillaries around follicles

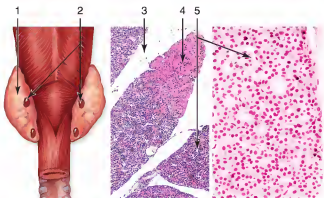
**Key Points:** The main features and functions of the thyroid **follicular cells** are as follows:

- They are well-stained epithelial cells, ranging in shape from squamous to low columnar and composing most of the simple epithelium of the thyroid follicles.
- They synthesize thyroglobulin and secrete it at their apical ends, forming most of the **colloid in the follicular lumen**.
- They pump iodide ions into the lumen and produce enzymes that iodinate tyrosine residues of thyroglobulin and conjugate these residues to form precursors for the active thyroid hormones  $T_4$  (thyroxine) and  $T_3$  (triiodothyronine).
- The processed thyroglobulin is then phagocytosed by the follicular cells, which degrade it in lysosomes and release free  $T_3$  or  $T_4$ , which in turn help regulate metabolic rates in target cells.
- Upon release from the follicular cells, these thyroid hormones are taken up by **perifollicular capillaries** for distribution in the blood.

Less numerous, more pale-staining cells derived from the embryonic neural crest, the **parafollicular cells** (or **C cells**), are scattered singly or in small groups between the thyroid follicles or among follicular cells. Parafollicular cells secrete the polypeptide hormone calcitonin, which is involved in regulation of blood calcium levels.

**Clinical Note:** Chronic dietary iodine deficiencies inhibit thyroid hormone production, causing thyrotropic cells of the anterior pituitary gland to produce excess thyroid-stimulating hormone. This leads to excessive growth of thyroid follicles and enlargement of the thyroid gland, a condition known as **goiter**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 360-365 and 367-368.*



## PARATHYROID GLANDS

1. Thyroid gland
2. Superior pair of parathyroid glands
3. Septum
4. Oxyphil cells
5. Principal cells (chief cells)

**Key Points:** The **parathyroid glands** are four small ( $3 \times 6$  mm) masses of endocrine tissue normally embedded in the connective tissue on the posterior surface of the **thyroid gland**. The **superior and inferior pairs** of these glands are respectively derived from the third and fourth pharyngeal pouches of the embryo. Connective tissue of the enclosing capsule forms **septa** subdividing each parathyroid gland into several lobules and contains more adipose tissue with aging.

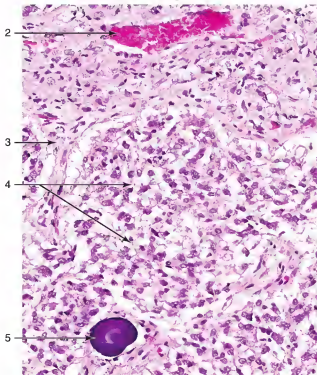
The most abundant cells in the parenchyma are the **principal (or chief) cells**, which are small cells with round nuclei and lightly stained acidophilic cytoplasm with numerous small granules containing the polypeptide parathyroid hormone (PTH). This hormone targets osteoblasts and indirectly increases blood calcium levels. PTH and calcitonin have generally opposing effects.

Parathyroid glands may also have variously sized clusters of larger, more acidophilic cells called **oxyphil cells**. These cells contain large numbers of mitochondria, become more numerous with age, and seem to be transitional derivatives of principal cells.

**Clinical Note:** In **hypoparathyroidism**, diminished secretion of PTH can cause bones to become more mineralized and denser and striated muscle to exhibit abnormal contractions due to inadequate calcium ion concentrations. Excessive PTH produced in **hyperparathyroidism** stimulates osteoclast number and activity, leading to increased levels of blood calcium, which can be deposited pathologically in cartilage, arteries, or the kidneys.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 365-367 and 369.*

1. This section is from what organ?



## PINEAL GLAND

1. Pineal gland
2. Venule
3. Septum
4. Pinealocytes
5. Corpus arenaceum (brain sand)

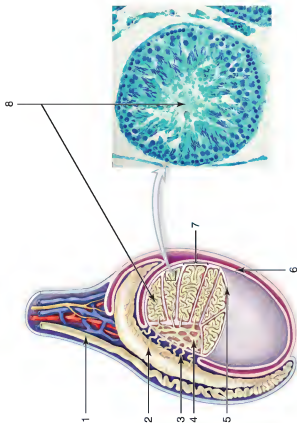
**Key Points:** The **pineal gland**, or epiphysis, is a very small, pine cone-shaped organ 5 to 8 mm long, attached by a short stalk to the brain near the posterior end of the third ventricle. It is covered by connective tissue of the pia mater, with **septa** forming smaller lobules and containing most of the arterioles, **venules**, and capillaries.

The secretory cells of this gland, called **pinealocytes**, are abundant, slightly basophilic cells with prominent nuclei and long cytoplasmic processes extending to the capillaries. Pinealocytes produce melatonin, a tryptophan derivative, whose release is promoted by darkness and inhibited by daylight via indirect neural connections with cells in the retina. This causes diurnal fluctuations in melatonin levels, which help set the circadian rhythms of physiologic functions and behaviors.

Among the pinealocytes are scattered astrocytes, also known as interstitial glial cells, which are difficult to see in routine preparations. Also present are characteristic small concretions of calcium and magnesium salts called **corpora arenacea**, or brain sand, which are of unknown physiologic significance and increase in both size and number with age.

**Clinical Note:** Densely calcified corpora arenacea can be used as landmarks for the midline location of the pineal gland in various **radiologic examinations** of the brain. **Tumors** originating from pinealocytes are very rare but can be either benign or highly malignant.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 367-370.*



## TESTIS AND GENITAL DUCTS

1. Ductus (vas) deferens
2. Epididymis
3. Efferent ductules
4. Rete testis
5. Tunica albuginea
6. Tunica vaginalis (visceral layer)
7. Lobule
8. Seminiferous tubules

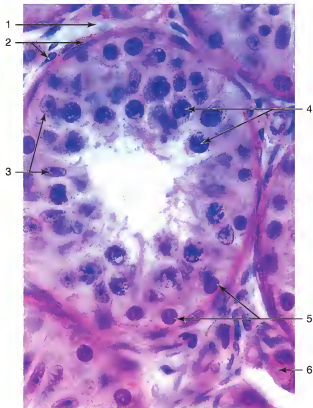
**Key Points:** One testis is suspended within each half of the scrotum. This sac is lined by a serous membrane, the parietal layer of the **tunica vaginalis**, continuous with the serous lining of the peritoneal cavity from which the testes migrate during fetal development. The visceral layer of this tunic forms the outer covering of each testis.

The dense fibrous capsule of each testis is the **tunica albuginea**, from which numerous thin connective tissue **septa** extend to a posterior thickening of fibrous tissue called the mediastinum testis. The septa subdivide the organ into approximately 250 **lobules**.

Each lobule contains from one to four **seminiferous tubules**, each of which is a long (average 50 cm), highly folded loop of spermatogenic epithelium where progenitor cells for sperm proliferate, undergo meiosis, and differentiate. The ends of the seminiferous tubules lead into the **rete testis**, a labyrinth lined by simple cuboidal epithelium embedded in the fibrous mediastinum testis. The rete testis is drained by 10 to 20 efferent ductules, which carry sperm into the **epididymis** for storage. At ejaculation, sperm are moved from each epididymis into a **ductus deferens**, or vas deferens, which leads to organs in the peritoneum. Each ductus deferens is bundled with the testicular blood vessels, lymphatics, and nerves into the spermatic cord.

**Clinical Note:** An excessive accumulation of serous fluid in one or both sides of the scrotal sac, termed a **hydrocele**, is the most common cause of scrotal swelling and a condition easily corrected surgically. **Cryptorchidism**, the failure of one or both testes to descend from the abdomen, occurs in approximately 4% of male neonates, but in most of these individuals, the testes move to the scrotum during the first year. Bilateral cryptorchidism causes infertility if not surgically corrected by 2 to 3 years of age.

See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 371-373.





## SEMINIFEROUS TUBULE AND INTERSTITIAL TISSUE

1. Interstitial tissue
2. Myoid cells
3. Supporting (Sertoli) cells
4. Primary spermatocytes
5. Spermatogonia
6. Interstitial (Leydig) cells

**Key Points:** Within each testicular lobule, the seminiferous tubules are supported by a stroma or **interstitial tissue** rich with fenestrated capillaries and steroid-secreting **interstitial cells**, or **Leydig cells**. At puberty these cells begin to produce testosterone under the influence of luteinizing hormone (LH). Testosterone promotes sperm formation and development of the secondary sexual characteristics. Surrounding the basement membrane of each seminiferous tubule are numerous contractile **myoid cells**, which contract to help move sperm and fluid along the tubule.

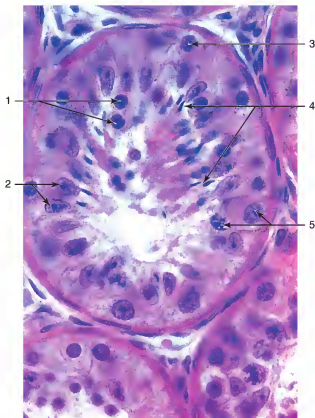
The wall of seminiferous tubules consists of spermatogenic epithelium containing mostly the germ cells, which are associated with fewer nurse or **supporting cells** often called **Sertoli cells**. Under the influence of follicle-stimulating hormone (FSH) at puberty, Sertoli cells begin to secrete androgen-binding protein, which increases the local concentration of testosterone. Occluding junctions between Sertoli cells help form a blood-testis barrier preventing access of immune cells and antibodies to the developing germ cells.

Key stages of spermatogenesis seldom appear in one tubular cross-section but include the following:

- Small, mitotically active cells called **spermatogonia** are in contact with the basal lamina.
- After a few rounds of mitosis, some of these cells enter meiosis, move toward the lumen, and become larger **primary spermatocytes**. These have large spherical nuclei and remain in the meiotic prophase for 3 weeks, during which time chromosomes undergo synapsis and recombination, before dividing to make two secondary spermatocytes.
- Secondary spermatocytes divide again almost immediately (making them relatively rare), each producing two haploid spermatids that differentiate into mature sperm cells.

**Clinical Note:** **Interstitial cell tumors** and **Sertoli cell tumors** are both rare. Most (95%) **testicular cancer** involves **germ cell tumors**, which only appear after puberty and are much more likely to develop in men with untreated cryptorchidism.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 373-379.*



## SEMINIFEROUS TUBULE

1. Spermatids
2. Supporting (Sertoli) cells
3. Spermatogonium
4. Differentiating sperm cells
5. Primary spermatocytes

**Key Points:** Different regions along the length of a **seminiferous tubule** contain different proportions of germ cells in the various stages of spermatogenesis. However, throughout the tubule **spermatogonia**, **primary spermatocytes**, the rare secondary spermatocytes, the small haploid **spermatids**, and the smaller **differentiating sperm cells** at the lumen all remain in close association with **supporting (Sertoli) cells** until their development is complete.

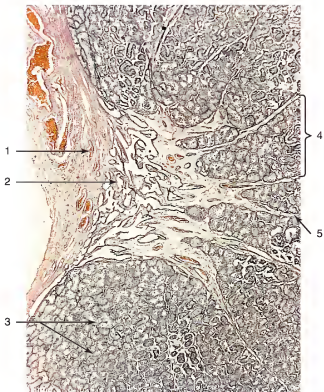
Sperm differentiation, or spermiogenesis, involves the following important steps:

- Chromatin becomes highly condensed, and the nucleus becomes elongated and flattened.
- The Golgi apparatus forms a large acrosome, filled with various hydrolytic enzymes and covering one end of the nucleus for use during fertilization, when the enzymes digest a path through the layers surrounding the oocyte.
- A perinuclear basal body opposite the developing acrosome produces the axoneme for an elongating flagellum.
- Mitochondria congregate at and wrap around the proximal portion of the flagellum, forming a thickened sheath where adenosine triphosphate (ATP) for flagellar movement is produced.
- Other cytoplasmic regions are no longer needed, are pinched off and phagocytosed by the Sertoli cells.

During both spermatogenesis and spermiogenesis, most developing male germ cells remain linked by cytoplasmic bridges that form by incomplete mitotic and meiotic divisions.

**Clinical Note: Decreased semen quality**, which is frequently idiopathic (arising from unknown causes), is a major cause of **male infertility**. Common features of poor quality semen include **oligospermia** (ejaculate volume <2 mL), sperm cell density less than 10 to 20 million/mL, abnormal sperm morphology, and flagellar defects that impair sperm motility.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 373-379.*



## RETE TESTIS AND INTRATESTICULAR DUCTS

1. Mediastinum testis
2. Rete testis
3. Seminiferous tubules
4. Lobule
5. Septum

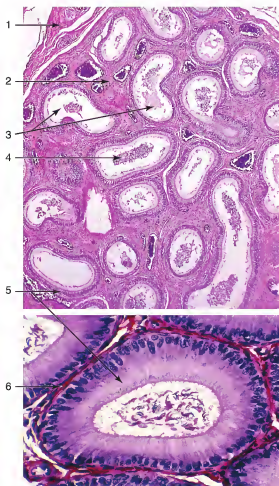
**Key Points:** The intratesticular ducts, which carry sperm from the **seminiferous tubules** in each **lobule** to the epididymis, are located near the **mediastinum testis**, the fibrous region that connects the **septa** between the many lobules. These ducts include three kinds of structures:

- Short straight tubules (or tubuli recti) extend from the ends of the seminiferous tubules and connect to the rete testis. Epithelium of the straight tubules lacks germ cells and consists only of Sertoli cells.
- The **rete testis**, an interconnected network of channels lined by simple cuboidal epithelium, is a prominent feature embedded in the connective tissue of the mediastinum testis.
- Sperm cells are moved from the rete testis to the epididymis via some 15 or 20 efferent ductules. These are lined by alternating patches of tall ciliated cells and cuboidal cells with microvilli, which give the epithelium of efferent ductules a distinct scalloped appearance in section.

Sperm are moved passively through these ducts and channels; they appear fully differentiated but are not yet completely mature or motile.

**Clinical Note:** Acute or chronic inflammation of the testis, **orchitis**, frequently involves the ducts connecting this organ to the epididymis. Common forms of orchitis are produced by infective agents and occur secondarily to a **urinary tract infection** or a **sexually transmitted pathogen** such as *Chlamydia* or *Neisseria gonorrhoeae* entering the testis from the epididymis or via the lymphatics.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 373 and 380-381.*



## EPIDIDYMIS

1. Tunica vaginalis
2. Stroma or interstitium with blood vessels
3. Duct of epididymis
4. Sperm cells
5. Pseudostratified columnar epithelium
6. Muscular layer

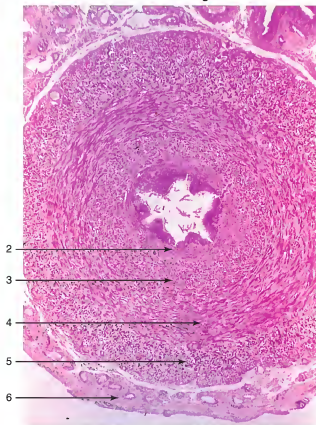
**Key Points:** Sperm cells are moved out of the rete testis through the small efferent ductules into the **epididymis**, a site for maturation and temporary storage of **sperm cells**. Located along the superior and posterior sides of each testis, each epididymis is covered by a connective tissue capsule and part of the **tunica vaginalis**. Within a vascularized stroma, the duct of each epididymis is a single tube more than 4 m long that is highly coiled into the head, body, and tail regions of the organ. Efferent ductules enter in the large head region, and the ductus deferens connects at the end of the tail.

The **duct of the epididymis** is lined by **pseudostratified columnar epithelium**. The tall columnar cells have long apical stereocilia that facilitate absorption of water from the fluid carrying sperm from the rete testis. The duct is surrounded by a well-defined **smooth muscle layer** that contracts at ejaculation to move sperm cells out of the duct of the epididymis into the ductus deferens. During the 2 to 3 weeks that sperm cells move through the epididymis, they mature and become capable of fertilizing an oocyte. Maturation includes completion of components for cell motility as well as membrane changes required for important sperm-egg interactions.

**Clinical Note:** Acute **epididymitis** is usually a result of **sexually transmitted infections** and causes intrascrotal pain and tenderness. Persistent inflammation of the epididymis, such as that associated with **gonorrhea** infections, includes massive invasion by leukocytes into the infected duct, stimulating fibrosis that obstructs the epididymis, and is a common cause of **male infertility**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 381-382.*

1. This is a cross-section of what organ?





## DUCTUS (VAS) DEFERENS

1. Ductus deferens
2. Mucosa
3. Inner longitudinal layer of muscularis
4. Middle circular layer of muscularis
5. Outer longitudinal layer of muscularis
6. Connective tissue of adventitia

**Key Points:** During ejaculation, a **ductus deferens** (**vas deferens**) transports sperm from each epididymis to the abdominal cavity where secretions from accessory glands are mixed with the sperm to produce semen. A part of the spermatic cord, the ductus deferens is a long straight tube with a **mucosa** lined by pseudostratified columnar epithelium with sparse stereocilia and a thin, elastic lamina propria.

Forceful and rapid peristaltic movement of sperm is produced by the **muscularis**, the thickest portion of the ductus wall, with smooth muscle arranged into:

- an **inner layer** with fibers running longitudinally next to the mucosa;
- a **middle layer** with fibers disposed in a circular manner; and
- an **outer layer** with fibers again running longitudinal.

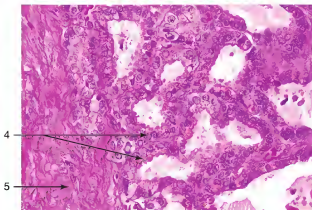
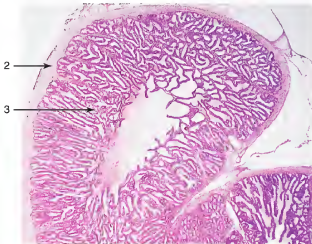
The muscularis is surrounded by a layer of fibroelastic **connective tissue**.

**Clinical Note:** Few serious medical problems occur in the ductus (vas) deferens, but these ducts allow for the most common surgical method of male contraception: **vasectomy**. In this procedure, a very small incision is made through the scrotal skin near the two ducts, each vas is exposed and cut, and the two ends (or only the end leading to the abdomen) are cauterized and tied.

After vasectomy, sperm are still produced, but they degenerate and are removed by macrophages in the epididymis (and in the scrotal sac when the short portion of the vas is left open-ended). Inflammatory and other pathologic changes occur in the mucosa of the epididymis, but serious adverse effects of vasectomy are usually minimal. A vasectomy may be reversed by surgically reconnecting the two ends of each ductus deferens. However, even successful surgery often fails to restore fertility due to incomplete sperm maturation in the epididymis changed by postvasectomy inflammation.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 381-383.*

1. What organ is this?



## SEMINAL VESICLE

1. Seminal vesicle
2. Muscularis
3. Mucosa
4. Secretory epithelium
5. Smooth muscle

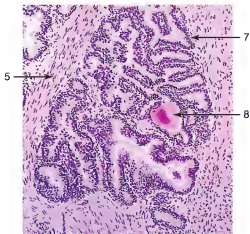
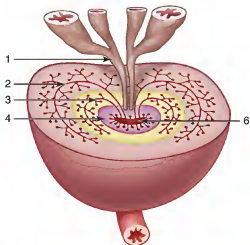
**Key Points:** The paired **seminal vesicles** are large accessory exocrine glands of the male reproductive tract that produce approximately 60 to 70% of the ejaculate. Secretory products of the glands include fructose and other metabolites for the sperm, fibrinogen for semen coagulation, and various enzymes and other substances. Each seminal vesicle empties into an enlarged ampulla portion of the ductus deferens where it becomes the ejaculatory duct before entering the prostate gland.

The seminal vesicles are each highly coiled tubes about 15 cm long. The most obvious histologic feature of the seminal vesicle is the **mucosa** with long, thin, very numerous, and complex folds that fill most of the lumen. The folds contain a thin layer of connective tissue and smooth muscle. They are lined by a variable simple or pseudostratified low columnar **secretory epithelium**, with the cells having neither cilia nor stereocilia.

Surrounding this mucosa is a thick **muscularis** with numerous interwoven bundles of **smooth muscle** that contract during ejaculation. This forces the secreted product of the gland into the ejaculatory ducts where it mixes with sperm being carried up the ductus deferens.

**Clinical Note:** Neoplasia and other serious medical problems with the seminal vesicles are very rare. Male infertility as a result of **low semen volume** may rarely be due to **agenesis** of one or both seminal vesicles or their failure to develop properly. Both seminal vesicles are normally removed during **prostatectomy**, a procedure in which their connections to the ejaculatory ducts and urethra are lost.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 383-384.*



## PROSTATE GLAND

1. Ejaculatory ducts
2. Peripheral zone
3. Central zone
4. Transitional zone
5. Smooth muscle
6. Prostatic urethra
7. Secretory epithelium and lamina propria
8. Corpus amylaceum

**Key Points:** The other major accessory gland contributing to semen is the **prostate gland**, a compact, fibrous organ approximately  $2 \times 3 \times 4$  cm in size and weighing about 20 g. It is located immediately below the urinary bladder and surrounds the urethra.

The prostate contains 30 to 50 small tubuloacinar glands embedded within a dense fibromuscular stroma and is surrounded by a thick capsule. The **secretory epithelium** of these glands is simple or pseudostratified columnar, and ducts from all the glands connect to the centrally located **prostatic urethra**. The glandular part of the prostate is sometimes subdivided into concentric but poorly demarcated areas with the following features:

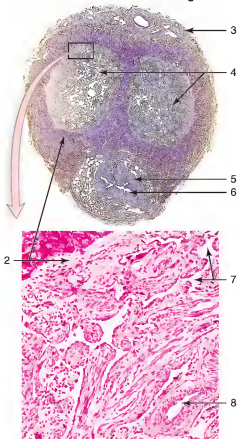
- The main glands have the longest ducts, being located in the wide **peripheral zone**, which occupies 70% of the prostate.
- Submucosal glands are in a **central zone**, occupying approximately 25% of the gland.
- The mucosal periurethral glands of the small **transitional zone** empty directly into the urethra.

Within many glands are small concretions of secreted material called **corpora amylacea**, a histologic marker for the prostate gland. Surrounding all these glands is **smooth muscle**, which contracts to empty the glands at ejaculation.

**Clinical Note:** The prostate gland is prone to three problems: (1) **chronic prostatitis**, usually involving bacteria or other infectious agents; (2) **nodular hyperplasia** or **benign prostatic hypertrophy**, often occurring in the mucosal or submucosal glands where it can lead to compression of the urethra and problems with urination; (3) **prostate cancer** (adenocarcinoma), the most common cancer in men, occurring mainly in glands of the peripheral zone.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 383-386.*

1. This is a cross-section of what organ?



## PENIS

1. Penis
2. Tunica albuginea
3. Skin
4. Corpora cavernosa
5. Corpus spongiosum
6. Penile (spongy) urethra
7. Cavernous spaces
8. Helicine artery

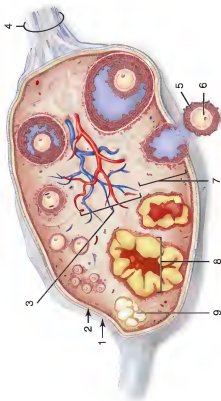
**Key Points:** The major components of the **penis** include the following:

- Two cylindrical masses, the dorsal **corpora cavernosa**, are each surrounded by a thick **tunica albuginea** of dense connective tissue and contain irregular vascular spaces separated by smooth muscle and fibroelastic trabeculae.
- A similar ventral mass, the **corpus spongiosum**, has a thinner tunic and surrounds the **penile** or spongy **urethra**. The urethral mucosa has large longitudinal folds and contains many small, scattered mucous glands. The corpus spongiosum extends to the end of the penis, expanding distally as the glans.
- Over most of the penis, thin **skin** covers a layer of loose connective tissue, which contains large blood vessels dorsally. The skin forms a major fold or prepuce covering the glans and continues as a very thin, sensitive layer directly over the glans itself.

The vascular **cavernous spaces** of the corpora cavernosa and corpus spongiosum receive blood from many small, coiling **helicine arteries**. The process of erection begins when parasympathetic stimulation causes the helicine arteries to dilate and the cavernous spaces fill with blood, enlarging all three masses of cavernous or erectile tissue. This enlargement first compresses the venules draining the spaces and eventually also occludes the larger dorsal veins outside the tunica albuginea. With continued entry of blood and minimal venous drainage, the penis becomes tumescent, rigid, and ready to deposit semen in the vagina.

**Clinical Note:** Erectile dysfunction, or **impotence**, can be the result of diabetes, anxiety, vascular disease, or nerve damage during prostatectomy. **Sildenafil** can alleviate the disorder by enhancing activity of factors mediating the neural effect on the helicine arteries.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 386-387.*





## OVARY

1. Surface epithelium
2. Tunica albuginea
3. Medulla
4. Suspensory ligament
5. Corona radiata
6. Ovulated secondary oocyte
7. Cortex with follicles
8. Corpus luteum
9. Corpus albicans

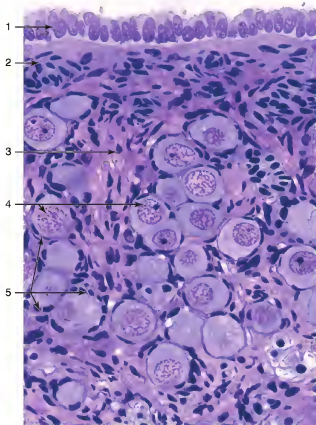
**Key Points:** Each ovary includes the following major areas:

- The centrally located **medulla** consists mostly of stroma and contains the branching ovarian artery and vein, which enter after passing along the **suspensory ligament**.
- The medulla is surrounded by the larger **cortex**, which includes various structures:
  - ovarian **follicles** in stages ranging from primordial to mature;
  - follicles in atresia, a degenerative process in which the cells undergo apoptosis;
  - an endocrine organ, the short-lived **corpus luteum**; and
  - **corpora albicans**, which are connective tissue remnants of former corpora lutea.
- The connective tissue capsule, the **tunica albuginea**, is covered by a simple cuboidal or low columnar epithelium, called the **surface epithelium** (or germinal epithelium), continuous with the mesothelium lining the peritoneum.

At ovulation, a mature follicle disrupts the weakened tunica albuginea locally and ruptures, releasing a **secondary oocyte** and cells attached to it that make up the **corona radiata**.

**Clinical Note:** Ovarian cysts are a common cause of enlarged ovaries and may interfere with ovulation. Derived from follicles or corpora lutea, ovarian cysts are usually benign, fluid-filled sacs ranging from 1 to 5 cm in diameter. If cyst formation disrupts blood vessels, blood enters the fluid, often rapidly, producing a **hemorrhagic cyst**. Ovarian cysts are usually asymptomatic but can produce unilateral pelvic or lower back pain.

See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 388-390.



## OVARIAN CORTEX AND PRIMORDIAL FOLLICLES

1. Surface epithelium
2. Tunica albuginea
3. Stroma of cortex
4. Primary oocytes in primordial follicles
5. Follicular epithelial cells

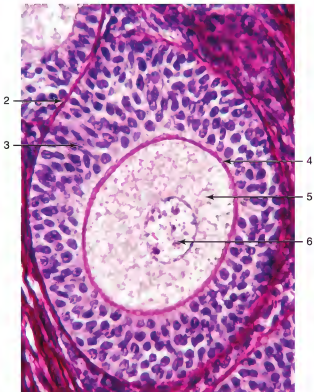
**Key Points:** The **surface epithelium** covering the ovary is continuous with the mesothelium lining the peritoneal cavity and covering other organs located there. Over the ovary, however, this epithelium assumes a cuboidal or low columnar morphology and is often misnamed the germinal epithelium, although its cells have no relationship with the ovarian follicles or germ cells.

Beneath the connective tissue of the **tunica albuginea**, the cortical **stroma** contains **primordial follicles**, all of which formed late in fetal development. The most immature and typically most abundant type of ovarian follicle, primordial follicles each consist of one large (25  $\mu\text{m}$  diameter) **primary oocyte**, which is arrested in the first meiotic prophase, and surrounding squamous **follicular epithelial cells** forming a layer around the oocyte.

**Clinical Note:** Like the developing follicles, the surface epithelium of the ovaries may produce **benign cysts**. However, this epithelium is also the most frequent source of **ovarian cancer**, one of the most common gynecologic malignancies. Sometimes called **epithelial tumors**, cancers of this type are of variable malignancy but have a high mortality rate because they are seldom detected early enough to be treated successfully.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 388-391.*

1. This ovarian follicle is in what stage?



## LATE PRIMARY FOLLICLE

1. Primary follicle
2. Basement membrane
3. Granulosa cells
4. Zona pellucida
5. Primary oocyte
6. Nucleus

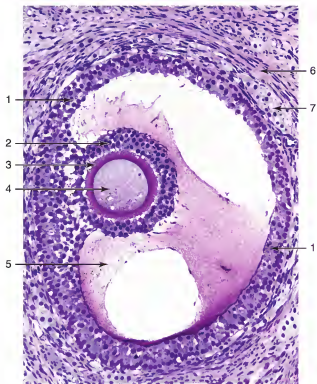
**Key Points:** Beginning at puberty under the influence of follicle-stimulating hormone (FSH), some primordial follicles enter a period of growth and development as **primary follicles**, which have the following features:

- The oocyte remains arrested in meiosis as a **primary oocyte** but enlarges greatly and has a large, transcriptionally active **nucleus**.
- The surrounding follicular cells, now called **granulosa cells**, are also larger, cuboidal, and more metabolically active, forming additional layers inside a **basement membrane**. Interconnected to one another and to the oocyte by gap junctions, granulosa cells transfer nutrients and various other macromolecules into the growing oocyte.
- Beneath the innermost layer of granulosa cells, a thick layer of extracellular material called the **zona pellucida** is secreted by the oocyte. It contains glycoproteins important for sperm binding.

Around the growing primary follicle, stromal cells begin to form cellular layers of the follicular theca. As the follicle continues to grow, granulosa cells proliferate and form a stratified cuboidal epithelium. Eventually, fluid-filled vesicles appear among the granulosa cells, and as growth continues, these vesicles gradually merge to form a large antrum. Follicles in which the antrum is forming are often called vesicular, antral, or secondary follicles. The growing oocyte remains a primary oocyte. Atresia of follicles is common at any stage.

**Clinical Note:** Growing primary follicles can become involved in **polycystic ovary syndrome (PCOS)**, which is characterized by enlarged ovaries with numerous cysts and an anovulatory state (with no follicles completing maturation successfully). The clinical presentation of this disorder is variable, and the etiology is unclear, although increased androgen production by the ovaries or adrenals is likely involved. Overall, PCOS is one of the most common causes of **infertility** in women.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 389–391.*



## ANTRAL FOLLICLE

1. Granulosa cells
2. Corona radiata
3. Zona pellucida
4. Primary oocyte
5. Antrum
6. Theca externa
7. Theca interna

**Key Points:** A late antral follicle is near maturation and has the following features:

- A single large **antrum** is present, filled with protein-rich fluid from the granulosa cells.
- A stratified epithelium composed of **granulosa cells** completely encloses the antrum and extends inward at one area (the cumulus oophorus) to form the **corona radiata** around the **zona pellucida** of the (still) **primary oocyte**.
- The stromal thecal layers immediately surrounding the basement membrane of the follicle are now differentiated as two tissues:
  - The **theca interna**, closest to the follicle, contains several layers of endocrine, steroid-secreting cells and is well vascularized.
  - The **theca externa** is an outer layer of fibrous connective tissue and smooth muscle fibers.

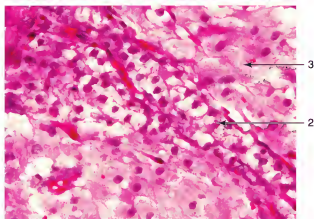
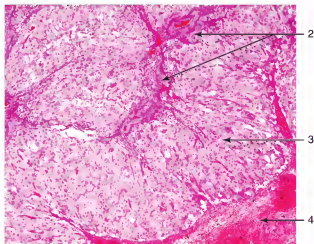
Cells of the theca interna synthesize progesterone and androstenedione, with the latter diffusing to the neighboring granulosa cells, which convert it to estradiol. These steroid hormones leave the follicle and are distributed in the blood throughout the body.

The mature or preovulatory follicle is approximately 20 mm in diameter, bulges against the tunica albuginea, and releases proteolytic enzymes that weaken this capsule. Just before ovulation, the oocyte completes the first meiotic division to produce the secondary oocyte and a polar body. With continued production of antral fluid, the mature follicle ruptures both the follicular wall and ovarian surface, releasing the oocyte with the corona radiata. These events are triggered by a surge in luteinizing hormone (LH) that occurs just prior to ovulation.

**Clinical Note:** Late primary or antral follicles can produce **follicular cysts**, which are thin-walled, fluid-filled structures with both granulosa and thecal endocrine cells. Follicular cysts are common and produce high estrogen levels, which can lead to menstrual irregularities.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 390-394.*

1. What is this ovarian structure?





## CORPUS LUTEUM

1. Corpus luteum
2. Theca lutein cells
3. Granulosa lutein cells
4. Clotted blood (hemorrhagic body)

**Key Points:** After ovulation, the empty follicle collapses but with the influence of LH the cells quickly reorganize to form the larger **corpus luteum**, a temporary endocrine gland specialized for steroid hormone production. Two cells types make up this gland, both derived from cells associated with the former follicle:

- The granulosa cells increase greatly in size and are now more heavily involved in steroid synthesis, becoming the **granulosa lutein cells** that comprise most (80%) of the gland.
- Cells of the former theca interna are now called **theca lutein cells**, which are much smaller and much less numerous than the other cells and are located along the sparse, vascularized connective tissue of the gland's internal folds.

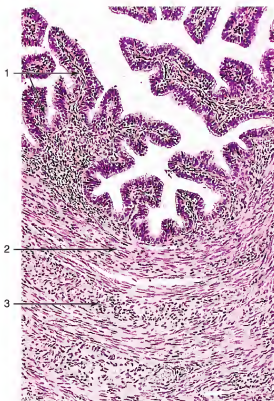
**Clots of blood** (hemorrhagic bodies) are another typical feature found deep within corpora lutea, forming when the microvasculature of the thecae is ruptured at ovulation.

Theca lutein cells increase production of progesterone, which causes the tissues in the uterine lining to develop in preparation for an embryo's possible arrival there. Granulosa lutein cells more actively produce estrogens from androstenedione, which continues to be synthesized by the theca lutein cells.

If there is no embryo to produce the gonadotropic hormone needed to maintain the corpus luteum, both types of luteal cells undergo apoptosis after 10 to 12 days, causing a decline in progesterone levels, and the gland shrinks and regresses (in a process not to be confused with follicular atresia). When the regression is complete, a small mass of collagen-rich connective tissue remains called the corpus albicans.

**Clinical Note:** Occurring less frequently than follicular cysts but still common, **corpus luteal cysts** result from delayed regression of the large corpus luteum. Continued progesterone production at elevated levels leads to menstrual irregularities, and large luteal cysts can rupture, causing hemorrhage into the abdominal cavity and acute pelvic pain.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 393-397.*



## UTERINE (FALLOPIAN) TUBE OR OVIDUCT

1. Mucosa
2. Circular layer of smooth muscle
3. Longitudinal layer of smooth muscle
4. Ciliated columnar cells
5. Secretory columnar cells

**Key Points:** The **uterine tubes**, also called Fallopian tubes or oviducts, are muscular tubes extending from the upper left and right sides of the uterus toward the ovaries. The wall of each uterine tube undergoes cyclic changes, especially in the mucosa, and includes the following:

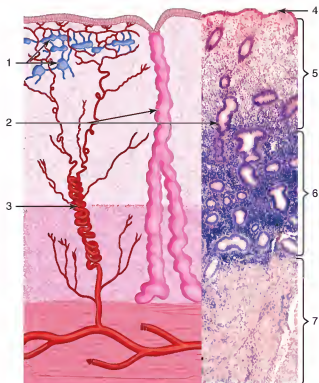
- The **mucosa** is characterized by many branched folds which extend far into the lumen. The lamina propria is covered by simple columnar epithelium consisting primarily of interspersed:
  - **ciliated columnar cells**, which help move both the sperm and the embryo; and
  - **secretory columnar cells**, which produce a nutrient-rich mucus.
- The muscularis is thick and contains two interwoven layers of smooth muscle: an **inner circular or spiral layer** and an **outer longitudinal layer**. Peristalsis aids movement of the oocyte and embryo toward the uterus.
- Most of the oviduct length is covered by a thin connective tissue layer and serosa.

Along the length of each uterine tube are four main regions:

- The large, open, funnel-shaped structure, the infundibulum, is open to the peritoneal cavity and is fringed by large fingerlike structures, the fimbriae, which at ovulation move over the ovary surface to facilitate movement of the oocyte into the tube.
- Each infundibulum leads to a long region with the widest diameter called the ampulla, where the oocyte undergoes either fertilization or degeneration.
- The next region, the isthmus, is also long, but narrower, with reduced mucosal folds.
- The final uterine or intramural part penetrates the thick wall of the uterus.

**Clinical Note:** **Tubal ligation** is a common surgical type of contraception. The uterine tube mucosa can become inflamed if infectious agents ascend from the lower genital tract, producing a condition named **salpingitis** after another name for these tubes: the **salpinges**. Mucosal damage or adhesions caused by chronic salpingitis can lead to **infertility** or an **ectopic (tubal) pregnancy** if there is blockage of embryo transport to the uterus.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 395-399.*



## UTERUS

1. Lacunae
2. Uterine glands
3. Spiral artery
4. Simple columnar epithelium
5. Functional layer of endometrium
6. Basal layer of endometrium
7. Myometrium

**Key Points:** The **uterus** is a pear-shaped organ with a wall of three layers, each continuous with its counterpart in the uterine tubes: a fibrous outer perimetrium covered largely by serosa; a thick middle smooth muscle layer, the **myometrium**; and a mucosal **endometrium**. The lining of the uterus changes radically during the menstrual cycle and shows these major features:

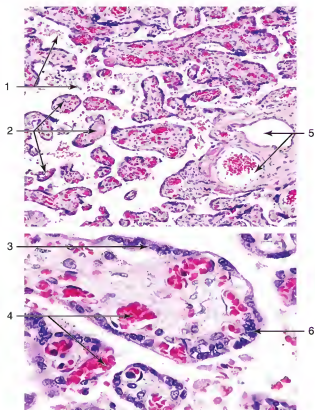
- The stroma of the endometrium is very rich in ground substance and reticulin fibers and is divided into a superficial **functional layer** and a more cellular **basal layer**.
- The **simple columnar epithelium** covering the endometrium is continuous with that of long **uterine glands**, which extend down through the basal layer as far as the myometrium.
- From arteries in the myometrium, smaller, progesterone-dependent **spiral arteries** enter the endometrium and branch in superficial areas of the functional layer to form microvasculature with many thin-walled **lacunae**.

The periodic changes in the endometrium can be summarized as follows:

- The preovulatory proliferative phase involves rapid elaboration of the functional layer from the basal layer and formation of the long uterine glands.
- The postovulatory, progesterone-dependent secretory phase, in preparation for blastocyst embryo implantation, involves thickening of the superficial layer, nutritive mucus filling the glands, and full development of the spiral arteries and vascular lacunae.
- The menstrual phase, triggered by declining progesterone levels during luteal regression, involves collapse of the spiral arteries and subsequent ischemia, disintegration, and sloughing of blood and tissue in the superficial layer.

**Clinical Note:** Viable endometrial cells frequently undergo menstrual reflux into or through the uterine tubes. In some women, this can lead to **endometriosis**, a disorder with pelvic pain or infertility due to endometrial tissue growing on the ovaries, oviducts, or elsewhere.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 396-403.*



## TERM PLACENTA

(Image by Dr. Alvin Telser.)

1. Maternal blood in venous lacuna
2. Branches of chorionic villi
3. Syncytiotrophoblast
4. Sinusoids with fetal blood
5. Extraembryonic arteriole and venule
6. Aggregate ("knot") of syncytiotrophoblast nuclei

**Key Points:** The fully developed placenta contains thousands of **branched chorionic villi**, most of which are suspended in large, **blood-filled lacunae** in the decidua, the stroma of the endometrium during pregnancy. Other villi serve to anchor the placenta to the decidua. The connective tissue in the villi is mesenchymal and surrounds components of the extraembryonic vasculature, including **arterioles**, **venules**, and the very numerous **sinusoids with fetal blood**.

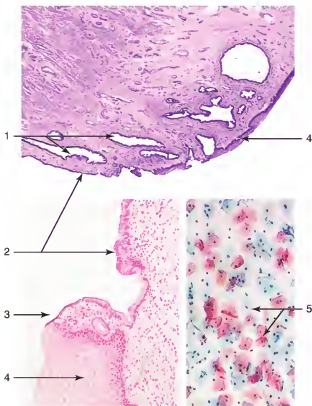
Initially, villi are covered by a two-layer epithelium derived from the trophoblast, the extraembryonic portion of the blastocyst:

- Immediately surrounding the connective tissue is the cytotrophoblast, which in early pregnancy has one layer of cuboidal cells.
- The outer layer is a thin, multinucleated syncytium of fused cells called the **syncytiotrophoblast**.

During the second trimester of the pregnancy, the inner cytotrophoblast layer begins to degenerate, and eventually the villi are covered only by the thin syncytiotrophoblast. This layer shows areas with **aggregated syncytial nuclei** (syncytial knots) and other extremely thin areas where it directly contacts the endothelium of the underlying sinusoids. Millions of the very thin areas with syncytiotrophoblast and closely associated sinusoidal endothelium collectively comprise the "placental barrier," across which exchange of  $O_2$ ,  $CO_2$ , nutrients, and wastes occurs between fetal blood in the sinusoids and maternal blood bathing the villi.

**Clinical Note:** **Gestational trophoblastic disease** is a term that includes various conditions caused by implantation of a blastocyst with an abnormal complement of chromosomes, such as triploidy caused by two sperm fertilizing an oocyte. Although such an embryo dies early in its development, cells of the trophoblast may proliferate and cover large villi in benign placental growths, such as **hydatidiform moles**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 403–406.*





## UTERINE CERVIX

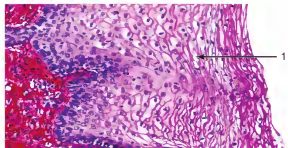
1. Cervical glands
2. Simple columnar epithelium of endocervical mucosa
3. Squamocolumnar junction between endocervix and exocervix
4. Stratified squamous epithelium of exocervix
5. Exfoliated normal squamous cells from exocervical mucosa

**Key Points:** The **cervix** is the narrow inferior portion of the uterus that projects into the superior region of the vagina. The endocervical mucosa surrounds the cervical canal and is lined by **simple columnar epithelium** and has mucus-secreting **cervical glands** but does not undergo the major cyclical changes or periodic sloughing seen in the endometrium. The exocervical mucosa covers the vaginal portion of the cervix and has thick, nonkeratinized **stratified squamous epithelium** like that of the vagina. An abrupt **squamocolumnar junction** is present at the boundary of these two epithelial types.

The position of the squamocolumnar junction shifts during a woman's reproductive life and after childbirth, and the area involved with these shifts is termed the transformation zone. Epithelial cells of this zone undergo metaplasia from columnar to squamous morphology. Because such changes can lead to potentially precancerous epithelial dysplasia, **squamous cells exfoliated** by scraping this cervical area are routinely sampled during medical exams.

**Clinical Note:** Routine screening by **exfoliative cytology** to check for dysplasia of the cervical epithelium, a test called the **Pap smear** after its developer George Papanicolaou, has greatly reduced the incidence of **cervical cancer** worldwide. The epithelial dysplasia that precedes **squamous cell neoplasia**, the most common type of cervical cancer, occurs in metaplastic cells of the transformation zone at a mean age of 54 years. These cells are readily infected by the **human papillomas virus**, which is strongly implicated, among other factors, in the pathogenesis of this cancer.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 405-407.*



## VAGINA

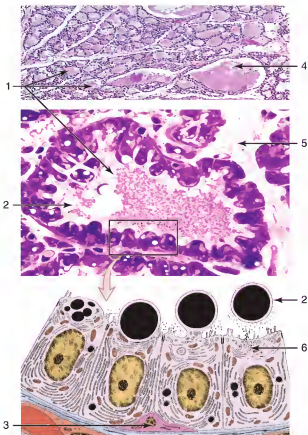
1. Nonkeratinized stratified squamous epithelium
2. Lamina propria
3. Muscularis

**Key Points:** The wall of the vagina lacks glands and has the following three layers:

- a mucosa with thick **nonkeratinized stratified squamous epithelium** and a thin **lamina propria**, papillae of which project into the epithelium;
- a **muscular layer** with poorly defined inner circular and outer longitudinal layers of smooth muscle; and
- an outer adventitia.

**Clinical Note:** **Atrophic vaginitis** involves thinning or atrophy of the vaginal epithelium caused by diminished estrogen levels and occurs most often in postmenopausal woman. This change allows the more frequent inflammation and infections characteristic of this condition. Primary **squamous cell carcinoma** of the vagina occurs rarely, with most vaginal malignancies having spread secondarily from the cervix or vulva.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, page 408.*



## LACTATING MAMMARY GLAND

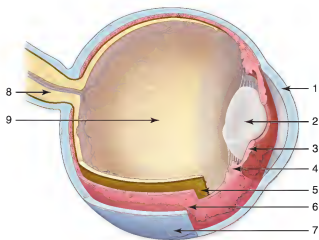
1. Secretory alveoli with milk
2. Lipid droplets in lumen
3. Myoepithelial cell
4. Lactiferous duct
5. Connective tissue of stroma
6. Secretory vesicles

**Key Points:** Each of the paired mammary glands consists of 15 to 25 lobes of the compound tubuloalveolar type, radially distributed around the nipple and separated by **connective tissue**. Glands in each lobe drain to the nipple by a separate **lactiferous duct**. Development of these glands and their intralobular ducts, along with formation of adipose tissue in the stroma, begin at puberty under the influence of estrogen and progesterone, causing the size increase in the breasts. During pregnancy, when progesterone and estrogen levels remain high and with the added influence of prolactin and other hormones, full development of functional glands is completed, with milk secretion, or lactation, beginning shortly before birth.

In the lactating mammary glands, the **secretory alveoli** and ducts contain milk, composed of water, proteins, lipid droplets, and nutrients secreted by cells of the alveoli. The secretory alveolar epithelium consists of large cuboidal cells active in the formation of **secretory vesicles** with proteins for secretion by exocytosis (merocrine secretion) and large **lipid droplets**, each of which is released from a cell apically with a covering of cell membrane (apocrine secretion). Plasma cells in the stroma produce IgA antibodies that are also transferred into milk. The secretory alveoli are surrounded by processes of **myoepithelial cells**, whose contractions help move milk into the ducts. Smooth muscle fibers in the wall of the lactiferous ducts and the lactiferous sinuses near the nipple are also important for milk ejection. After weaning, cells of the secretory alveoli undergo apoptosis, and the duct system formed during pregnancy involutes.

**Clinical Note: Breast cancer** most often originates from epithelial cells of the ducts in or near the glands. The most common form is invasive **ductal carcinoma** in which neoplastic cells of intralobular ducts or small branches of lactiferous ducts invade the surrounding stroma, forming a fixed, palpable mass. Bacterial infection of a mammary gland, or **acute mastitis**, may occur in the lactating or involuting breast, usually after obstruction of the duct system by milk.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 408-411.*



## LAYERS AND MAJOR STRUCTURES OF THE EYE

1. Cornea
2. Lens
3. Iris
4. Ciliary body
5. Retina
6. Choroid
7. Sclera
8. Optic nerve
9. Vitreous body

**Key Points:** The many parts of the eye are organized into three layers:

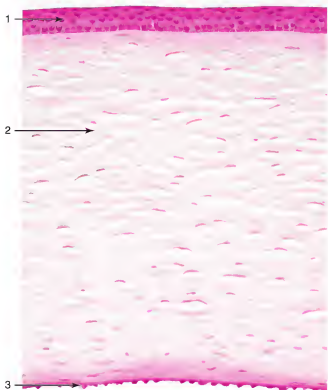
- The outermost fibrous layer consists of the anterior **cornea** and the posterior **sclera**.
- The middle vascular layer, or uvea, consists of the **choroid** lining the sclera, the **ciliary body** extending from the choroid just inside the corneoscleral junction, and the **iris**, which extends from the ciliary body anterior to the lens and has a central opening, the pupil.
- The innermost **retina**, where photoreception occurs, lines the choroid and is continuous with the **optic nerve**, which penetrates the choroid and sclera as it exits the eye.

In addition to the components of these layers, the eye contains the following structures:

- The **lens**, a transparent structure surrounded by the ciliary body focuses light entering through the pupil onto the retina.
- A large, transparent **vitreous body** of gel-like connective tissue fills a cavity posterior to the lens.
- Posterior to the cornea is a fluid-filled anterior cavity subdivided into an anterior chamber between the cornea and iris and a posterior chamber between the vitreous body and the iris.

**Clinical Note:** Eye disorders involving one or more of the diverse structures within the eye are common, and numerous systemic diseases can also cause ocular problems. All such disorders, as well as injuries to the eye, are treated by medical doctors specially trained in **ophthalmology**.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 412–414.*





## CORNEA

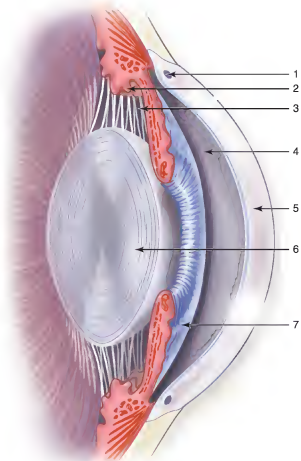
1. Corneal epithelium
2. Stroma (substantia propria) with keratocytes
3. Corneal endothelium

**Key Points:** The cornea is normally avascular and completely transparent. Three important tissue layers of this structure are as follows:

- The anterior **corneal epithelium** is a thin nonkeratinized stratified squamous epithelium continuous with the conjunctival epithelium covering the anterior part of the sclera. Stem cells for renewing the corneal epithelium are located around the circumference of the cornea near the corneoscleral junction, or limbus. The corneal epithelium includes the 8–10  $\mu\text{m}$  thick basement membrane called Bowman's membrane, or the anterior limiting membrane.
- Beneath this membrane is the **corneal stroma**, or substantia propria, which constitutes 90% of the cornea's thickness. The stroma consists of approximately 60 thin layers of parallel collagen bundles, with alternating layers at right angles. The collagen is synthesized and maintained by flattened cells called **keratocytes**, which also produce proteoglycans in small amounts of ground substance. At the limbus, the stroma does also contain very small blood vessels.
- The posterior surface is covered by the **corneal endothelium**, a simple squamous epithelium with a thick (10  $\mu\text{m}$ ) posterior limiting membrane often called Descemet's membrane. The corneal endothelium is bathed by aqueous humor in the anterior cavity and maintains the hydrated state of the corneal stroma that provides optimal transparency.

**Clinical Note:** Corneal grafts (transplants) between unrelated individuals can usually be accomplished successfully without immune rejection due in part to this tissue's lack of both a vascular supply and lymphatic drainage and to local immune tolerance produced by ocular antigen-presenting cells and immunomodulatory factors in aqueous humor. **Laser-assisted in situ keratomileusis (LASIK) surgery** involves reshaping the contour of the stroma, after exposing this layer via an epithelial flap, to correct **myopia** (near-sightedness), **hyperopia** (far-sightedness), or **astigmatism** (irregular curvature of the cornea).

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 413–416.*



## ANTERIOR CAVITY AND AQUEOUS HUMOR

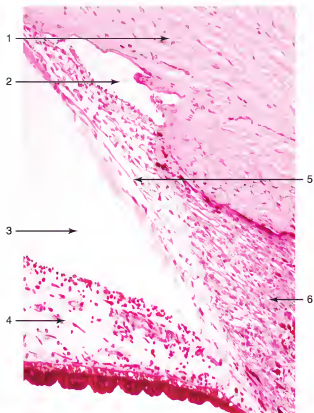
1. Scleral venous sinus
2. Ciliary processes
3. Posterior chamber of the anterior cavity
4. Anterior chamber of the anterior cavity
5. Cornea
6. Lens
7. Iris

**Key Points:** Immediately behind the cornea is the **anterior cavity**, with its posterior and anterior chambers containing aqueous humor, a clear and essentially protein-free liquid. Continuous production and removal of aqueous humor involves the following:

- Aqueous humor is produced as epithelial cells covering the **ciliary processes** transport water from the underlying, highly vascular stroma into the **posterior chamber**. These processes project into this chamber as folds from the surface of the ciliary body.
- The fluid fills the posterior chamber, bathing the **lens**, and flows through the pupil into the **anterior chamber**.
- At the angle between the **iris** and the **cornea**, aqueous humor passes through a trabecular meshwork covered by the endothelium that also lines the limbus and enters the **scleral venous sinus** (the canal of Schlemm), a circular channel that returns this fluid to blood in scleral veins.

**Clinical Note:** If more aqueous humor is produced than is drained, the excess can cause abnormally high intraocular pressure, or **glaucoma**, a significant cause of vision loss in the United States. If untreated, glaucoma can lead to impaired vision due either to pressure-induced degenerative changes in the retina and head of the optic nerve or to excessive corneal hydration causing that structure to become opaque. Most glaucoma patients can be treated successfully by topical drugs (eye drops), which diminish aqueous humor production, but in some cases, one of several surgical approaches can be used to enlarge the outflow channels to the scleral venous sinus.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 414-420.*



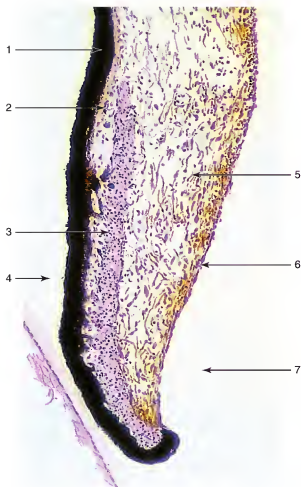
## SCLERAL VENOUS SINUS

1. Limbus (corneoscleral junction)
2. Scleral venous sinus (canal of Schlemm)
3. Anterior chamber
4. Iris
5. Trabecular meshwork
6. Ciliary body

**Key Points:** At the angle formed where the **iris** meets the **corneal limbus**, aqueous humor normally leaves the anterior chamber for its return to the blood. Here, the endothelium of the **anterior chamber** is not supported by the thick (Descemet's) basement membrane present on the posterior side of the cornea. Instead, this endothelium forms the delicate lining of small channels in the stroma of the **corneal limbus** and **ciliary body**. These channels make up the **trabecular meshwork** or reticulum and merge to form the larger **scleral venous sinus** (or canal of Schlemm), which is slightly deeper in the limbus. All of these structures involving drainage are continuous around the circumference of the cornea.

**Clinical Note:** When the iridocorneal angle is more narrow or acute than usual, thickening of the peripheral iris that occurs with dilation of the pupil can occlude the angle and obstruct drainage of aqueous humor at the trabecular meshwork. This can result in the rapid development of intraocular hypertension known as **angle closure glaucoma**, **acute glaucoma**, or **closed (narrow) angle glaucoma**. This condition usually affects both eyes and causes blurred vision, eye pain, and headache. Treatment of this type of glaucoma usually includes some form of surgical intervention.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 414–420.*



## IRIS

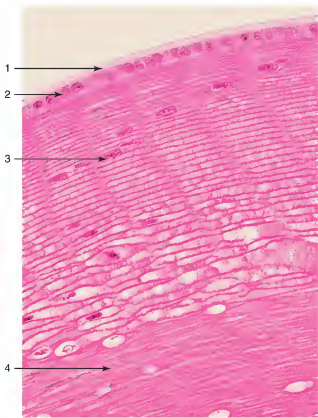
1. Epithelium of pigmented cells
2. Dilator pupillae muscle
3. Sphincter pupillae muscle
4. Posterior chamber (of the anterior cavity)
5. Stroma
6. Anterior limiting layer
7. Anterior chamber

**Key Points:** The **iris** is an anterior extension from the ciliary body and has a central opening, the **pupil**, in front of the lens. Major components of the iris include the following:

- The anterior iris surface, although bathed by aqueous humor in the **anterior chamber**, is not covered by epithelium, but by densely packed and interwoven fibroblasts and melanocytes forming the **anterior limiting layer**.
- The thick **stroma** contains microvasculature and various populations of melanocytes, which contribute to the variable color of this tissue.
- An **epithelium of pigmented cells** covers the posterior iris surface, in contact with aqueous humor of the **posterior chamber**. This heavily pigmented epithelium prevents light from passing through the iris, so that the only light reaching the retina must enter at the pupil and pass through the center of the lens.
- The iris epithelium includes numerous myoepithelial cells, containing less melanin, which comprise the **dilator pupillae muscle**. Contraction of the radial processes extending from these myoepithelial cells dilates the pupil.
- In the stroma surrounding the pupil, there is a large, circumferential bundle of smooth muscle cells, the **sphincter pupillae muscle**, which contracts to constrict the pupil.

**Clinical Note:** Inflammation of the iris, termed **iritis** or **anterior uveitis**, can result from blunt trauma to the eye or be associated with various systemic inflammatory diseases. This condition may produce pain and redness in the eye, an irregular or small pupil, and blurred vision. Iritis can lead to the complications of **secondary glaucoma** if the inflammation causes adhesions between the peripheral iris and tissue at the iridocorneal angle that interfere with drainage of aqueous humor.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 416-417 and 422.*





## LENS

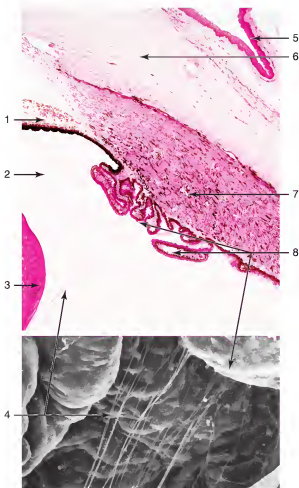
1. Lens capsule
2. Lens epithelium
3. Differentiating lens fibers
4. Mature lens fibers

**Key Points:** The **lens** is a transparent, avascular, resilient tissue that focuses light on the retina. It forms in the embryo from an invagination of the surface epithelium (ectoderm) and retains many epithelial characteristics. Major features of the lens include the following:

- Surrounding the lens is a thick (10–20  $\mu\text{m}$ ) **capsule**, an acellular layer of type IV collagen and proteoglycans produced as the basal lamina of the cells that form the lens.
- The anterior surface of the lens is covered by a simple cuboidal **epithelium** with the basal ends of the cells attached to the capsule.
- Most of the lens substance is composed of lens fibers, which differentiate from epithelial cells migrating internally at the equatorial (peripheral) area of the lens. **Differentiating lens fibers** become greatly elongated, gradually lose their organelles and nuclei, and become filled with proteins called crystallins that produce transparency. **Mature lens fibers** average only a few micrometers in diameter but may be several millimeters long and are aligned in a parallel manner. These fibers normally function for an individual's lifetime.

**Clinical Note:** Lens epithelial cells continue to form new lens fibers throughout life, compressing older fibers, displacing them into the center or nucleus of the lens, and causing the lens to enlarge and lose elasticity with normal aging (**presbyopia**). This diminishes the lens' ability to have its shape changed during accommodation and causes most people after the age of 40 years to require some means of **visual correction**, such as eye glasses, for activities that involve near vision. Later in life, clefts may appear between lens fibers and become filled with nontransparent material. This produces one or more areas of lens opacification that are termed **cataracts**. When vision is impaired by cataracts the lens can be removed, after which light is focused on the retina by corrective glasses or a prosthetic lens implant.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 417 and 423.*



## CILIARY BODY AND ZONULE

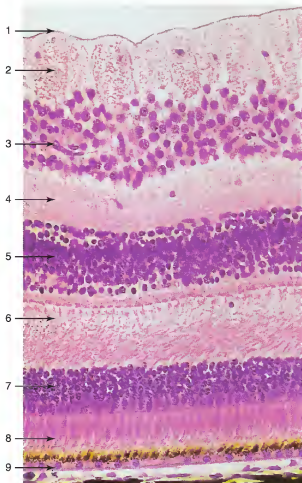
1. Iris
2. Posterior chamber
3. Lens
4. Zonular fibers
5. Conjunctiva
6. Corneoscleral junction (limbus)
7. Ciliary muscle
8. Ciliary processes

**Key Points:** The **lens** is held in place immediately behind the **iris** by the **ciliary zonule**, a set of fine fibers produced by cells at the surface of the surrounding **ciliary body**. This association with the ciliary body allows the focus of the lens to be changed for near and distant vision in the process of accommodation. Main points of this lens-ciliary body interaction include the following:

- The ciliary zonule (also called the suspensory ligament of the lens) consists of numerous radially oriented **zonular fibers** which project from between the **ciliary processes**, cross the **posterior chamber**, and insert into the lens capsule.
- Focusing the lens involves the action of the large mass of smooth **ciliary muscles** in the ciliary body. These muscles form the largest part of the ciliary body located just posterior to the **corneoscleral junction (limbus)**, which is covered externally by **conjunctiva**.
- In the eye at rest or focused on distant objects, the ciliary muscles are relaxed, which puts tension on the zonule and causes the lens to flatten slightly. To focus on nearby objects, the ciliary muscles contract, causing the zonule to relax and allowing the lens to assume its normal more spherical shape, or undergo accommodation.

**Clinical Note:** In modern cataract surgery, the lens is removed by aspiration of the lens substance while it is emulsified by a vibrating probe. The posterior side of the lens capsule and its inserted zonular fibers are left in place at the posterior chamber. The concave posterior capsule, or capsular bag, is then used as the site for implantation of an acrylic **intraocular lens (IOL)** prosthesis. Research is underway to develop IOLs capable of natural accommodation using the ciliary muscles.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 417 and 420-421.*



## RETINA

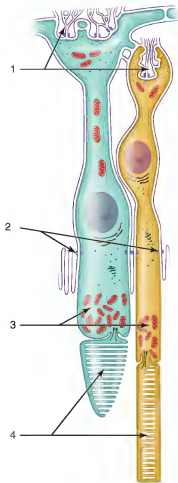
1. Inner limiting layer
2. Nerve fiber layer
3. Ganglionic layer
4. Inner plexiform layer
5. Inner nuclear layer
6. Outer plexiform layer
7. Outer nuclear layer
8. Rod and cone layer
9. Pigmented layer

**Key Points:** The **retina** is the site of photoreceptive neural cells that convert light into nerve impulses relayed to the brain for the sense of sight or vision. Light is refracted by the lens and vitreous body onto the retina, where it passes through several layers before reaching the photoreceptive rod and cone cells. From the vitreous body these layers are as follows:

- the extremely thin **inner limiting layer**, which is the basal lamina of the astrocytic (Müller) cells that organize and support the neurons of the retina;
- the much thicker **nerve fiber layer** containing axons of cells in the next layer, which will converge at the optic disc to form the optic nerve;
- the **ganglionic layer** with the nucleated cell bodies of the ganglion cells (neurons);
- the **inner plexiform layer** containing a dense network of synaptic processes from the ganglion cells and the various neurons of the next layer;
- the **inner nuclear layer** with cell bodies of various neurons and of the astrocytic cells;
- the **outer plexiform layer** with the network of processes from the rod and cone cells and those from neurons of the inner nuclear layer;
- the **outer nuclear layer** containing the nucleated cell bodies of the rod and cone cells;
- the **rod and cone layer** with the light-sensitive elongated outer segments of these cells; and
- the outermost **pigmented layer** of the retina, a simple epithelium of cuboidal cells with long microvilli that surround the outer segments of the rod and cone cells.

**Clinical Note:** Trauma to the head or eye can cause a **detached retina**, a medical emergency in which the neural layers become separated from the outermost pigmented layer.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 418–427.*



## ROD AND CONE CELLS

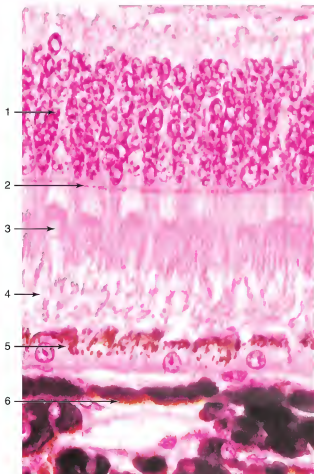
1. Synapses in outer plexiform layer
2. Junctions of outer limiting layer
3. Inner segments
4. Outer segments

**Key Points:** Rod cells and cone cells both have the following structural features:

- Processes that form **synapses in the outer plexiform layer** with processes from bipolar neurons of the inner nuclear layer.
- Aligned **adhesive junctions** between these cells and the apical ends of the astrocytic (Müller) cells, forming a faint line (called the **outer limiting layer**) just outside the outer nuclear layer that contains the nuclei of the rod and cone cells.
- **Inner segments** with cytoplasm containing abundant mitochondria and other organelles.
- Connected to the inner segments by short stalks with modified ciliary axonemes are the photoreceptive **outer segments**. In the more numerous rod cells, the outer segments are cylindrical, and in cone cells, they are shorter and conical. Both rods and cones are filled with stacked membranous discs, which in cones are continuous with the cell membrane. The lipid bilayers of these membranes contain the opsin proteins that bind retinal and respond to light by initiating a process that produces impulses transmitted to neurons of the inner nuclear layer. In rods, the light-sensitive protein is rhodopsin, whereas cones contain one of three types of iodopsin sensitive to red, green, or blue light.

**Clinical Note:** Partial **color blindness** is normally an inherited disorder due to recessive mutations in genes for one or more iodopsins or other genes required for cone function. The most common form, **red-green color blindness**, affects the cones responsible for detecting light at these two wavelengths and occurs much more frequently in men than women because many key genes for the color sensitivity are on the X chromosome. With two X chromosomes, women do not usually show the disability but can be carriers of the mutation.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 418–427.*





## RETINA AND CHOROID

1. Outer nuclear layer
2. Outer limiting layer
3. Inner segments of rod and cone cells
4. Outer segments of rod and cone cells
5. Pigmented layer of retina
6. Choroid

**Key Points:** The interface of the retinal and vascular layers shows more detail of the following structures:

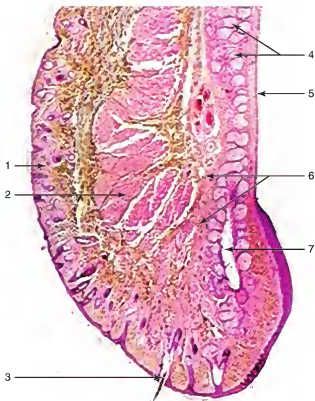
- the **outer nuclear layer** containing nuclei of the rod and cone cells;
- the very thin **outer limiting layer** showing the aligned adhesive junctions between the photoreceptive cells and the supporting astrocytic cells;
- the region containing the **inner segments** of the rod and cone cells;
- the region with the photosensitive rod and cone **outer segments**;
- the **pigmented layer of the retina**; and
- the highly vascular **choroid** layer, which contains connective tissue components and a large number of melanocytes.

The retina's pigmented layer is simple cuboidal epithelium, with melanin granules present mainly in the apical microvilli, which extend among the rod and cone outer segments. These epithelial cells have several functions, including: to contribute to the blood-retinal barrier, to phagocytose shed membranous discs from rods and cones, to isomerize retinal for use in the rods and cones, and to absorb light passing through the layer of rod and cone cells. Choroid tissues help bring nutrients and  $O_2$  to the rod and cone cells and absorb light passing through the retina.

Lateral to the optic disc is a small round retina area called the macula lutea. This surrounds the fovea in which the inner layers of the retina are not present and the photoreceptive layer consists mostly of cones. These differences make the fovea the area of greatest visual acuity.

**Clinical Note:** Age-related macular degeneration, a very common cause of blindness in the elderly of developed countries, includes thinning and depigmentation of the pigmented retina layer at the macula, loss of retina and choroid capillaries in this area, and degeneration of the photoreceptor cells in the fovea.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 418–427.*



## EYELID

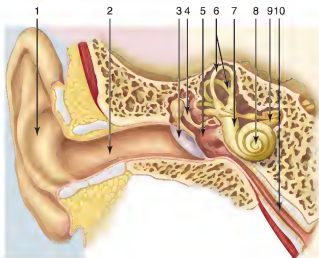
1. Skin
2. Striated muscle
3. Eyelash
4. Tarsal (sebaceous) glands
5. Conjunctiva
6. Fibroelastic connective tissue (tarsus)
7. Duct of tarsal sebaceous glands

**Key Points:** The **eyelids** function to protect and shade the eyes and include the following tissues:

- The outer surface is covered by thin **skin**, with a prominent row of large hair follicles for **eyelashes** at the periphery.
- The middle of the eyelid contains fascicles of the large **striated muscle**, the orbicularis oculi muscle.
- A **layer of fibroelastic connective tissue** called the **tarsus** provides structural support and surrounds a series of large **sebaceous tarsal glands**, which are drained by large **ducts** to the edge of the eyelid.
- Covering the tarsal glands, the inner lining of the eyelid is part of the **conjunctiva**, a mucosa consisting of a stratified columnar epithelium with small mucus-secreting cells and a thin lamina propria. The conjunctiva of the eyelids is continuous, covering the anterior surface of the sclera.

**Clinical Note:** **Conjunctivitis**, or **pink eye**, is a condition in which the conjunctiva is inflamed usually due to bacterial or viral infection or to allergies. The inflammation increases the discharge of mucus and enlarges the microvasculature of the scleral conjunctiva, causing the sclera to have a reddish appearance. Bacterial and viral conjunctivitis are both contagious but usually have little effect on vision.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 423-424 and 429.*



## EAR

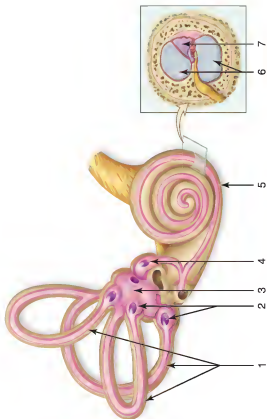
1. Auricle of external ear
2. External acoustic meatus
3. Tympanic membrane
4. Auditory ossicles
5. Tympanic cavity of middle ear
6. Semicircular canals
7. Vestibule
8. Cochlea
9. Cochlear branch of cranial nerve VIII, the vestibulocochlear nerve
10. Auditory (eustachian) tube

**Key Points:** The ears contain mechanoreceptors for both hearing (auditory function) and equilibrium (vestibular function). Each ear has three major regions:

- The **external ear** consists of:
  - the **auricle**, or pinna, an irregular, skin-covered plate of elastic cartilage
  - that funnels sound waves into the **external acoustic meatus**, a canal lined by skin with sebaceous glands and modified apocrine sweat glands called ceruminous glands.
- The **tympanic cavity of the middle ear**, lined mainly by simple cuboidal epithelium,
  - is separated from the acoustic meatus by the lateral **tympanic membrane** (eardrum), which vibrates in response to sound waves;
  - communicates on the anterior side with the pharynx via the **auditory tube** (eustachian or pharyngotympanic tube); and
  - contains a series of articulating bones, the **auditory ossicles**, which transfer vibrations of the tympanic membrane to produce fluid movements in the internal ear.
- The internal ear includes three complex, communicating, membrane-lined regions: the **vestibule**, the set of three **semicircular canals**, and the **cochlea**. All these regions contain sensory cells in synapses with fibers of the **vestibulocochlear nerve**.

**Clinical Note:** The middle ear tympanic cavity may show inflammation (**otitis media**), especially in young children, when viral or bacterial infections extend there from the upper respiratory tract via the auditory tubes.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 425–427 and 430.*



## INTERNAL EAR

1. Semicircular canals and ducts
2. Ampullae of semicircular ducts
3. Utricle
4. Sacculle
5. Cochlea
6. Perilymph in bony labyrinth of cochlea
7. Endolymph in cochlear duct

**Key Points:** Like the posterior part of the middle ear, all three regions of the **internal ear** are enclosed within the temporal bone of the skull. This complex **bony labyrinth** is filled with fluid called **perilymph** and contains a similar shaped **membranous labyrinth** lined by epithelium and filled with another fluid, **endolymph**. A cross-section through one turn of the cochlea shows the endolymph-filled **cochlear duct**, which is part of the membranous labyrinth, supported by two perilymph-filled regions of the bony labyrinth.

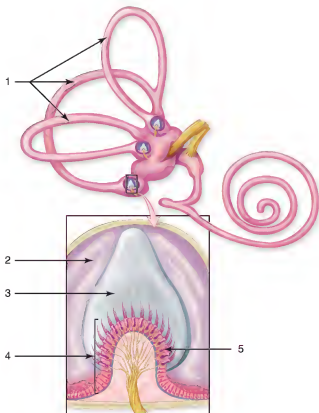
The central area of the internal ear, the vestibule, is divided into two parts:

- the **utricle**, which connects to all three **semicircular ducts** near their enlarged portions, called **ampullae**; and
- the **sacculle**, which connects to the **cochlear duct**.

In both the utricle and the sacculle, the epithelial lining (the vestibular labyrinth) includes thicker regions (maculae) with columnar hair cells, mechanoreceptors which detect movement of calcified structures called otoliths (or otoconia) embedded within a gelatinous region of the endolymph. Sensations transmitted to the brain from these cells provide information needed to maintain the body's equilibrium, specifically regarding the direction of gravity relative to the head and the linear acceleration of the head.

**Clinical Note:** The sensation of **vertigo** or dizziness associated with rapid head movements can also be produced by internal ear inflammation (**vestibular neuritis**) or neurologic conditions that cause dysfunctional activity of the vestibular system. **Ménière disease** involves episodes of vertigo accompanied by hearing loss and ringing in the ears (**tinnitus**) and is caused when increased pressure within the membranous labyrinth (**endolymphatic hydrops**) leads to rupture and leakage of endolymph into the perilymph.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 427-434.*





## SEMICIRCULAR DUCTS AND AMPULLAE

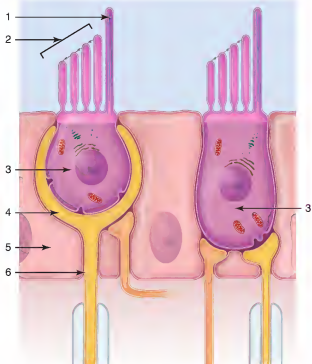
1. Semicircular ducts
2. Endolymph
3. Cupola
4. Crista ampullaris
5. Hair cells and supporting cells

**Key Points:** The **semicircular ducts and ampullae** also play a major role in the vestibular function of the internal ear. These membranous structures are located in the three semicircular canals of the bony labyrinth, which lie at approximately right angles to each other. The enlarged ampulla of each duct is located near its connection to the utricle and has a region with hair cells in its epithelial lining where movement of the endolymph is detected.

In each ampulla, the wall forms a ridge called the **crista ampullaris** covered by epithelium with **mechanoreceptor hair cells** and their columnar **supporting cells**. The apical ends of hair cells have modified stereocilia and cilia that project into an overlying elongated layer of proteoglycans in the **endolymph** called the **cupola**. The cupola is attached to the membranous wall opposite the crista and moves with the movement of endolymph in the semicircular duct. This movement affects the hair cells' synaptic connections with sensory fibers of the vestibulocochlear nerve, producing sensations with information for vestibular regions of the brain regarding angular or rotational movements of the head.

**Clinical Note:** Brief periods of vertigo produced by sudden changes in position of the head, such as standing up quickly or sitting up after lying in bed, may be examples of **benign paroxysmal positional vertigo (BPPV)**. This condition results when one or more of the dense, calcified otoliths detach from the gelatinous membrane in the utricle and lodge as "**canaliths**" in one of the cristae ampullares or semicircular ducts, producing an abnormal stimulus on the hair cells in that crista. A specific series of slow head movements in the **canalith repositioning procedure** can often be used to return the otoliths to the utricle and relieve the sensation of dizziness and unsteadiness.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 429-434.*



## HAIR CELLS

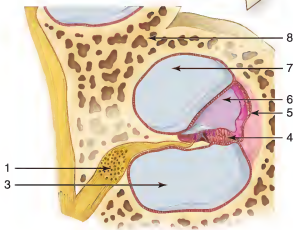
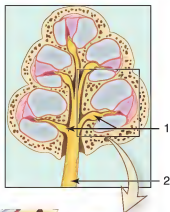
1. Kinocilium
2. Stereocilia
3. Hair cell
4. Calyx axonal ending
5. Supporting cell
6. Afferent nerve fiber (axon)

**Key Points:** The mechanoreceptor **hair cells** of the internal ear detect movements of endolymph produced by head movements or sound waves. They are surrounded by a variety of **supporting cells**, which both support the hair cells physically and sustain them metabolically. The basal end of each hair cell has one or more synaptic connections with afferent **sensory nerve fibers**. With type I hair cells, the end of the afferent axon forms a chalice-like **calyx** around the entire basal portion of the cell. Synaptic activity is modulated by an efferent nerve fiber that contacts either the afferent nerve calyx of type I hair cells or the hair cell directly (type II).

Hair cells are usually columnar and have at their apical ends a single long **kinocilium**, a typical primary cilium, and many **stereocilia** decreasing in length with distance from the kinocilium. The stereocilia and kinocilium are connected by various linking proteins, including long types of cadherin proteins composing the "tip links." Movements of the apical ciliary structures change the degree of tension in these links, which opens or closes ion channels and affects the synaptic activity of the hair cells.

**Clinical Note:** Various drugs can produce dose-related **ototoxic side effects** on the hair cells involved with both vestibular and auditory function. Aminoglycoside antibiotics can cause permanent damage and loss of function in hair cells. Certain other antibiotics, some diuretics, antimalarial drugs, and certain chemotherapeutic agents such as cisplatin can also damage the hair cells of the internal ear.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 427–429 and 432–435.*



## COCHLEA

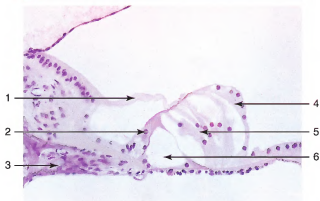
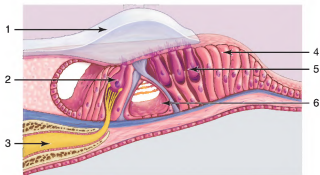
1. Spiral ganglion
2. Cochlear branch of cranial nerve VIII
3. Scala tympani
4. Spiral organ (of Corti)
5. Stria vascularis
6. Cochlear duct (scala media)
7. Scala vestibuli
8. Bone

**Key Points:** The **cochlea** mediates the auditory function of the internal ear. The membranous **cochlear duct**, also called the **scala media**, is approximately 3.5 cm long and emerges from the sacculle. It coils  $2\frac{3}{4}$  times within the bony labyrinth of the temporal **bone** around a core called the **modiolus**. Major features of the cochlea include the following:

- The **scala vestibuli** runs above the cochlear duct, and the **scala tympani** runs below the cochlear duct; both contain perilymph.
- The **stria vascularis** is situated along the lateral wall of the cochlear duct, where the lining is a unique stratified epithelium that surrounds capillaries from the periosteum and transfers water and ions from plasma to maintain the endolymph.
- The **spiral organ**, or organ of Corti, projects into the cochlear duct and is supported by the membrane that separates that duct from the scala tympani. Hair cells of the spiral organ initiate nerve impulses when they detect the fluid movements produced by the ossicles when sound waves hit the tympanic membrane. High-frequency sounds affect hair cells in the first part of the spiral organ, and sounds of progressively lower frequency affect hair cells farther along the spiral organ.
- The large **spiral ganglion**, located with the bony modiolus, contains the cell bodies of bipolar neurons. Dendrites of these cells are the afferent fibers contacting hair cells of the spiral organ, and their axons comprise the **cochlear branch of cranial nerve VIII** which enters the brain stem.

**Clinical Note:** Deafness can have various causes. **Sensorineural hearing loss** is due to disorders of sensory components of the cochlea, whereas **conductive hearing loss** stems from problems in the middle or external ear.

See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 430-431 and 434-438.



## SPIRAL ORGAN (ORGAN OF CORTI)

1. Tectorial membrane
2. Inner hair cells
3. Cochlear nerve
4. Supporting cells
5. Outer hair cells
6. Inner tunnel

**Key Points:** The **spiral organ (of Corti)** forms part of the membrane separating the cochlear duct from the scala tympani. Important features are present along the entire length of this organ and are seen best in cross-section:

- Several types of **supporting cells** surround different kinds of hair cells.
- **Inner hair cells** and **outer hair cells** are found on the two sides of the **inner tunnel**, which is formed by specific elongated supporting cells.
- Stereocilia of the hair cells are in contact with or are embedded in the **tectorial membrane**, an acellular layer of collagen and other proteins extending from the modiolus.
- Dendrites from the spiral ganglion innervate inner hair cells and form part of the **cochlear nerve** (the cochlear branch of cranial nerve VIII).

**Clinical Note:** Excessive stimulation of the cochlear hair cells by repeated, long-term exposure to loud sounds leads to **noise-induced hearing loss**, which may be temporary or permanent. Such overstimulation of the hair cells causes them to swell and undergo degenerative changes due in part to toxic effects of reactive oxygen species and damage to the cell membrane and stereocilia.

Some types of sensorineural hearing loss can be treated by a **cochlear implant**. A small cable with a series of electrodes is threaded into the scala tympani, with the electrodes along the wall containing branches of the cochlear nerve. A device containing a microphone and a transmitter is worn behind the external ear. Sounds of various frequencies cause transmission of signals to the electrodes that stimulate the nerves appropriate for those frequencies. Impulses from those nerves are interpreted in the brain as sounds. Cochlear implants do not restore normal hearing but can provide the deaf patient with a range of sounds that enables understanding and participation in speech.

*See Mescher AL, Junqueira's Basic Histology, 12th edition, pages 427, 434, and 436.*

## **Chapter 15**

Card 15-1 McKinley, Fig 26-9; Card 15-3 McKinley, Fig 19-6; Card 15-4 McKinley, Fig 19-7b; Card 15-5 McKinley, Fig 26-5; Card 15-7 (Top) Berman, Fig 12-16; Card 15-8 Berman Fig 12-18; Card 15-9 Berman, Fig 12-22; Card 15-14 McKinley, Fig 26-15; Card 15-19 McKinley, Fig 26-17a; Card 15-20 (Top) McKinley, Fig 26-17b, (Bottom) Berman, Fig 12-43

## **Chapter 16**

Card 16-1 (Top) McKinley, Fig 26-4, (Bottom) Berman Fig 13-29; Card 16-3 Berman, Fig 13-32; Card 16-5 (Bottom) Berman Fig 13-21; Card 16-8 Berman, Fig 13-7; Card 16-11 McKinley, Fig 26-21; Card 16-12 (Top) Berman, Fig 13-15

## **Chapter 17**

Card 17-1 (Top) McKinley, Fig 17-2; Card 17-2 (Top) McKinley, Fig 19-9; Card 17-3 Berman, Fig 14-1; Card 17-7 McKinley, Fig 25-9; Card 17-8 Berman, Fig 14-18; Card 17-9 (Bottom) McKinley, Fig 25-10; Card 17-11 (Top) McKinley, Fig 25-11

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Card 18-2 Berman, Fig 15-4; Card 18-3 (Top) Berman, Fig 15-2, (Bottom) McKinley, Fig 5-4a; Card 18-6 McKinley, Fig 5-9a; Card 18-7 McKinley, Fig 5-9b; Card 18-8 Berman, Fig 15-10; Card 18-11 (Bottom) McKinley, Fig 5-8

## **Chapter 19**

Card 19-1 McKinley, Fig 27-3; Card 19-2 McKinley, Fig 27-5; Card 19-3 McKinley, Fig 27-4; Card 19-4 McKinley, Fig 27-6a, b; Card 19-5 McKinley, Fig 27-6c; Card 19-10 McKinley, Fig 27-8b; Card 19-11 Berman, Fig 16-18

## **Chapter 20**

Card 20-1 McKinley, Fig 20-4; Card 20-2 McKinley, Fig 20-6; Card 20-3 Berman Fig 17-3; Card 20-4 Berman, Fig 17-4; Card 20-6 McKinley, Fig 20-13; Card 20-8 (Top) McKinley, Fig 20-9; Card 20-10 (Top) McKinley, Fig 20-11a, (Middle) Berman, Fig 17-17

## **Chapter 21**

Card 21-1 McKinley, Fig 28-13; Card 21-2 Berman, Fig 18-7; Card 21-3 Berman, Fig 18-8; Card 21-4 Berman, Fig 18-2; Card 21-5 Berman, Fig 18-14; Card 21-6 Berman Fig 18-16; Card 21-7 (Top) Berman Fig 18-18; Card 21-8 (Bottom) Berman, Fig 18-21; Card 21-9 (Top) Berman, Fig 18-23

## **Chapter 22**

Card 22-1 McKinley, Fig 28-4a; Card 22-2 McKinley, Fig 22-6; Card 22-6 Berman, Fig 19-16; Card 22-7 (Bottom) McKinley, Fig 28-7; Card 22-10 Berman, Fig 19-23; Card 22-11 (Top) Berman, Fig 19-26

## **Chapter 23**

Card 23-1 McKinley, Fig 19-12a; Card 23-3 McKinley, Fig 19-17; Card 23-5 Berman, Fig 20-4; Card 23-8 Berman, Fig 20-9; Card 23-12 McKinley, Fig 19-20; Card 23-13 McKinley, Fig 19-22; Card 23-14 McKinley, Fig 19-25; Card 23-16 McKinley, Fig 19-27a, b; Card 23-17 (Top) McKinley, Fig 19-27 d, (Bottom) Berman, Fig 20-19